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CHEMISTRY AND PHARMACY OF VEGETABLE DRUGS

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THE

CHEMISTRY AND PHARMACY

OF

VEGETABLE DRUGS

Dealing with the derivation and properties of all the principal Vegetable Drugs.

By

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PREFACE

THIS book is especially designed to answer the many questions which must arise in the mind of those interested in pharmacy when making preliminary acquaintance with the numerous vegetable drugs and their galenical preparations. Thus, in the discussions of drugs of secondary importance, the items have frequently been grouped together so that, although the descriptions are individually inadequate, the reader is enabled to assess the value of the medicaments in relation to the more important drugs and thereby acquire a useful perspective knowledge of the vegetable series. The marshalling of so many separate accounts into a connected narrative has presented obvious difficulties, but every endeavour has been made to sustain the reader's interest by occasionally widening the field of view and thus introducing discussions which properly belong to subjects not ordinarily treated in a discourse professedly devoted to vegetable drugs. No allusions have been made to disturbances in the supply of commodities occasioned by the war, since such references, besides being of little avail, would, with the passage of time, lose their significance.

The present-day student of materia medica is called upon to assimilate an ever-increasing number of facts concerning newly discovered hormones and synthetic drugs, but it is important to realise that very few of the medicaments of vegetable origin have been thereby displaced, whence it is essential for the medical practitioner and the pharmacist to acquire detailed knowledge concerning them. If this volume helps to this end it will have achieved its purpose.

In writing this work the British Pharmaceutical Codex has been of great value as a source of information concerning the less common drugs. The author desires to express his thanks to Mr. T. E. Wallis, B.Sc., F.I.C., Ph.C., for kindly lending the original photographs for Figures 1, 2, 5, and 6, and to Mr. A. I. Robinson, Ph.C., for the remaining illustrations in the chapter on opium, all of which are reproduced by courtesy of the Editor of *The Pharmaceutical Journal*. All the other photographic illustrations were taken in the laboratories and warehouses of The British Drug Houses Ltd., by kind permission of the Directors, while the author is indebted to his assistant, Mr. A. H. Abbott, B.Sc., A.I.C., for help in reading the proofs and for compiling the index. Finally, the author is particularly desirous to record his grateful thanks to Mr. R. R. Bennett, B.Sc., F.I.C., a Director of The British Drug Houses Ltd., and a Member of the British Pharmacopœia Commission, for his very kindly interest and valuable advice.

N. L. A.

CONTENTS

THE CHEMISTRY AND PHARMACY OF VEGETABLE DRUGS

Chapter I

CLASSIFICATION : GALENICALS : TESTS

IN the following pages it is proposed to describe medicaments occurring in the vegetable kingdom in contradistinction to medicines of mineral or animal origin and to organic drugs prepared synthetically in the laboratory. Plants which are cultivated in various parts of the world for their value as drugs owe their medicinal properties to particular constituents, to which the general term "active principle" is applied. Many of these active principles are extremely complex substances and their precise chemical nature is not yet known ; but even in those cases where the constitution of the important ingredient has been discovered, it is still generally more convenient to use the product prepared by nature rather than to employ an active ingredient prepared synthetically. However, the alternative procedure of administering the isolated active principle in preference to an extract of the whole plant is often adopted.

CLASSIFICATION

In order to present a coherent account of a large number of individual products some attempt at systematic grouping is essential and in the case of vegetable drugs there would appear to be three possibilities : namely, division according to their botanical classification ; the chemical nature of their active principles ; or their therapeutic action.

Of these alternatives, the most precise is the botanical, and the whole assemblage might be grouped according to the natural orders to which they severally belong, but, notwithstanding its scientific basis, the method is not well suited for the purpose of presenting the subject from the practical standpoint. Thus, most vegetable drugs as met with in commerce only consist of one portion of the plant, such as the root, leaf or seed whence its taxonomical characteristics are not apparent. Again, drugs belonging to the same natural order often have nothing else in common by which they can be associated ; for example, under the Leguminosæ one finds products so different, both chemically and therapeutically, as senna, liquorice, Calabar beans and cutch.

The grouping of drugs according to the chemical nature of their active principles is much more helpful to the student of practical pharmacy and, so far as its limitations allow, the method has been adopted in compiling this book. However, although many of the most valuable drugs have been subjected to exhaustive chemical investigation and the nature of their physiologically active constituents is well understood, there still remains a considerable number of vegetable medicaments, mostly of secondary importance but nevertheless of real value and quite extensively employed, which have not been sufficiently well examined to justify accurate chemical description.

On first consideration it might be thought that vegetable drugs could, after all, be most conveniently grouped according to their therapeutic applications, but even this method, notwithstanding its simple practical basis, is not completely satisfactory. The main difficulty attaching to this scheme lies in the fact that many of the most important drugs are employed for several different purposes : thus belladonna, according to the manner in which it is administered, behaves as an intestinal sedative, as an external anodyne or as an agent for temporarily enlarging the pupils ; again, cinchona, besides being the most important agent known to mankind for the control of malaria, is also a useful bitter tonic. On the other hand, a therapeutic classification is well suited as an aid for describing drugs which, generally, are only used for one specific purpose, and it has been adopted in this book as an adjunct to the chemical grouping. While many of the drugs discussed under a therapeutic heading may be regarded as of minor importance, this is by no means always the case, and the reader is asked to remember that, as no systematic scheme can be followed throughout, the various items are grouped in the manner which is most likely to assist in their study.

Chemical Classification

Vegetable drugs containing physiologically active principles which are referable to the chemical group known as alkaloids are by far the most important. These substances are nitrogenous bases which occur in plants combined with acids as salts and they are called alkaloids in allusion to their alkaline character. Most alkaloids are complex compounds containing carbon, hydrogen, nitrogen and generally, although not always, oxygen, and many of them have been determined chemically to be derivatives of one or other of three aromatic bases, namely, pyridine, quinoline and isoquinoline, all of which occur in coal-tar. More than two hundred vegetable alkaloids have been characterised, but only a fraction of these are employed medicinally, and many plants which have been shown to contain one or more of these bases are not used as drugs. In order to emphasise the important role which these bodies play in therapeutic science, it is only necessary to state that such products as

opium, cinchona, belladonna and ipecacuanha owe their medicinal worth to the alkaloids which they contain. General information concerning the principal alkaloidal drugs is given in Table I, and the next

TABLE I—DRUGS CONTAINING ALKALOIDS

Name	*Part of Plant Employed*	*Name of Principal Alkaloid*	*Approximate Percentage of Principal Alkaloid Present*	*Physiological Action*
Aconite ..	Root	Aconitine ..	0·2 to 0·8	Febrifuge (i.e., anti-fever).
Areca ..	Seed	Arecoline ..	—	Vermifuge (i.e., anti-worm).
Belladonna	Leaf	Hyoscyamine	0·4	Antispasmodic sedative, etc.
	Root	ditto ..	0·5 to 0·8	ditto.
Calabar bean	Seed	Physostigmine	0·15 to 0·3	Myotic.
Calumba ..	Root	Calumbamine Palmatine Jateorhizine	—	Bitter.
Cinchona ..	Bark	Quinine .. Cinchonine	3 to 5	Bitter and tonic, etc.
Coca ..	Leaf	Cocaine ..	0·1 to 1	Local anæsthetic (isolated alkaloid used).
Colchicum ..	Corm .. .. Seed	Colchicine .. ditto ..	0·3 0·5	Gout specific. ditto.
Conium ..	Leaf .. .. Fruit	Coniine ..	0·1 0·5 to 1	Sedative and antispasmodic.
Ephedra ..	Leaf and stem	Ephedrine ..	0·7	Sedative for asthma.
Ergot ..	Sclerotium ..	Ergometrine .. Ergotoxine ..	0·002 to 0·035 0·02 to 0·2	Arrests hæmorrhage.
Hydrastis ..	Rhizome ..	Hydrastine ..	2	Arrests hæmorrhage.
Hyoscyamus	Leaf	Hyoscyamine Hyoscine	0·08	Sedative.
Ipecacuanha	Root	Emetine ..	1·7	Expectorant and emetic.
Jaborandi ..	Leaf	Pilocarpine ..	0·5	Diaphoretic (i.e., producing perspiration).
Gelsemium ..	Root	Gelsemine ..	—	Nerve sedative.
Lobelia ..	Leaf and stem	Lobeline ..	—	Antispasmodic.

TABLE I—DRUGS CONTAINING ALKALOIDS—*continued.*

Name	*Part of Plant Employed*	*Name of Principal Alkaloid*	*Approximate Percentage of Principal Alkaloid Present*	*Physiological Action*
Nux vomica	Seed	Strychnine ..	1·2	Tonic.
Opium ..	Latex ..	Morphine ..	11	Narcotic and sedative.
		Codeine ..	1·5	
Pomegranate	Bark	Pelletierine ..	0·2	Anthelmintic (i.e., tending to expel intestinal worms).
Stavesacre ..	Seed	Delphinine ..	1	Destroys pediculi.
		Delphisine		
Stramonium	Leaf	Hyoscyamine	0·2 to 0·4	Antispasmodic.

eight chapters of this book are devoted to an account of such of these as conveniently conform to a chemical classification.

Another highly important group of active principles characterising certain vegetable drugs are known as glucosides. These compounds are distinguished by their property of undergoing decomposition in the presence of dilute mineral acids, or of certain enzymes, with the formation of a sugar and a residual substance of varying complexity. As an example, mention may be made of salicin, which occurs in willow bark : in aqueous solution this substance is hydrolysed by the enzyme emulsin, dextrose and saligenin being produced. The hydrolysing enzymes usually exist in the same parts of the plants as the glucosides, but the latter are not decomposed under natural conditions, because the glucosides and the enzymes are situated in separate cells and are thus kept apart by the walls of the cellular tissue. One of the most important drugs in this class is digitalis, or foxglove. The leaves of this plant contain complicated glucosides characterised by their property of stimulating the action of the heart, and thus it is invaluable to the physician in treating cases of cardiac failure.

Certain glucosides, when hydrolysed by means of dilute mineral acid or an enzyme, yield hydrocyanic acid (prussic acid) as one of the products of decomposition: thus, amygdalin, which occurs in bitter almonds, gives rise to hydrocyanic acid, dextrose and benzaldehyde. In small doses hydrocyanic acid is a useful digestive stimulant, and a group of vegetable products containing this particular type of glucoside are discussed together in this book under the heading of Cyanogenetic Drugs.

There is yet another class of glucosides of some importance in pharmacy known as the saponins. These substances form a soap-like froth when

shaken with water, and even extremely dilute solutions exhibit the phenomenon after being vigorously agitated. The saponins are powerful protoplasmic poisons and many are strongly sternutatory; on hydrolysis they yield various sugars, together with non-toxic compounds termed sapogenins. A separate chapter is devoted to a description of the more important vegetable drugs which owe their value to the saponins they contain.

The purgative drugs—cascara sagrada, frangula, rhubarb, senna and aloes—all contain principles which are closely allied in chemical constitution and are known as the emodins. These substances are chemical derivatives of anthraquinone which, in turn, is formed by the oxidation of anthracene, a hydrocarbon which occurs in the last portion of the distillate from coal-tar. The emodin of senna is trihydroxymethyl-anthraquinone, while that of rhubarb is dihydroxymethyl-anthraquinone, this latter substance being termed chrysophanic acid. The characteristic emodin of aloes, tetrahydroxymethyl-anthraquinone, or barbaloin, is known to exist in the plant as a glucoside, being combined with the sugar arabinose.

A large number of vegetable drugs contain physiologically active resins, and among these the most important are the purgatives, jalap, podophyllum and scammony root. Resins occur as solid, amorphous and generally vitreous masses having a conchoidal fracture and are insoluble in water and acids, but soluble in alcohol, ether and oil of turpentine. They dissolve in alkalis to form compounds of the nature of soap, being, with certain exceptions, again precipitated from the aqueous solutions of these on the addition of mineral acids.

The active constituents of a number of astringent vegetable drugs are referable to the tannins which is a generic name given to the naturally occurring derivatives of poly-hydroxybenzoic acids. Some tannins appear to contain derivatives of catechol, and are termed phlobo-tannins in contradistinction to those tannins originating from pyrogallol. Phlobotannins are characterised by the readiness with which they yield a red precipitate of phlobophane when their aqueous solutions are boiled with hydrochloric acid.

Therapeutic Classification

As already indicated, certain important drugs which are employed for one specific and well-defined purpose will be described under a therapeutic heading, even though the chemical nature of the active principle may be known. Thus, considering the drugs listed in Table I, it is more convenient for the purposes of study to include areca and pomegranate bark in a chapter devoted to a description of medicaments used for the expulsion of parasitic worms rather than endeavour to associate them with those containing alkaloids. Again, although the active principles of calumba are alkaloidal in chemical nature, it is more

usual to regard it as an important member of the group known as bitters, thus linking it with gentian, which owes its therapeutic value to the glucosides which it contains.

Again, the therapeutic classification is more convenient for those vegetable drugs employed as carminatives since the volatile oils upon which the action of most of them depend differ widely in chemical nature. Another objection to presenting a chemical grouping of the carminative drugs arises in the case of ginger which, although a highly important member of the series, owes its activity not to its volatile oil but to a complex mixture of phenolic substances collectively termed gingerol.

As further examples which can only be classified on a therapeutic basis may be mentioned such chemically diverse substances as mustard and capsicum which are both useful rubefacients. Among expectorants, ipecacuanha and squill are probably the most important, but as both these drugs are of great value for other purposes they have been described in relation to the chemical character of their active constituents, while a separate chapter is devoted to an account of the numerous other vegetable substances which are similarly employed for the stimulation of the respiratory tract. Finally, it may be remarked that so little is known concerning the chemistry of many minor vegetable drugs that a rational chemical classification of them would be impossible.

THE PREPARATION OF GALENICALS

It has already been observed that vegetable drugs as sold in commerce usually consist of some particular part separated from the whole plant such as the root, leaf, bark or whatever portion has been found by experience to possess therapeutic value in greatest degree. Some important drugs consist of juices or other exudations, but whatever the original substance may be it is necessary that it should be reduced to some form convenient for administration as a medicine. Occasionally the dried and powdered drug can be used, but more generally it is necessary to prepare an extract with some suitable solvent. The selection of the solvent is important, and the choice should be so made that the preparation contains the maximum amount of active principle coincident with the minimum proportion of physiologically inert material. The preparations so made are termed galenicals, and the manufacture of most of these follow general principles.

Methods of Powdering Drugs

After the plant material has been dried it is usually necessary, except in the case of soft exudations, to reduce it to powder before the galenicals can be made. For small-scale work an iron mortar and pestle is usually all that is required, but for manufacturing purposes various types of grinding mills have been devised. Mention may be made of the ball mill which consists

of a hollow cylindrical vessel horizontally mounted on bearings. This cylinder, made of unglazed porcelain or steel, is charged with the drug to be ground together with several balls also made of porcelain or steel; on being rotated by motor power the drug is gradually reduced to a fine powder.

Another type of mill is known as the end-runner and consists of a mechanically revolving mortar containing a pestle mounted on a vertical shaft and free to revolve by friction with the sides of the mortar (Fig. 1).

Fig. 1.—A SMALL END-RUNNER MILL USED FOR GRINDING SAMPLES OF DRUGS PREPARATORY TO THEIR ANALYSIS

Yet another type of mill called the edge-runner consists of two heavy wheel-shaped granite stones which are connected to a common axle and run on a shallow stationary granite bed. When the central shaft is made to revolve by a power motor the two granite rollers are moved with it and run on the bed and over any drug placed in their path. The motion of the stones forces the drug out on either side of the track, but it is brought back into the path of the stones by scrapers revolving on the same axis (Fig. 2).

In preparing galenicals the fineness of the powder is important, and it is therefore necessary to pass the material through standardised sieves as shown in Fig. 3.

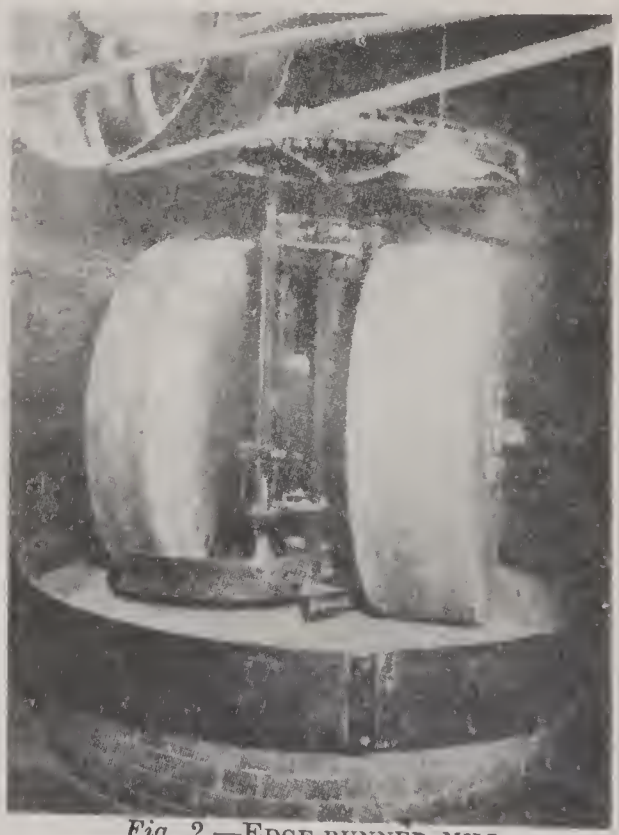


Fig. 2.—EDGE-RUNNER MILL
Each revolving stone weighs about 2½ tons.

Liquid Extracts

An extract is a preparation made by separating the soluble matter of the vegetable tissues by means of water or alcohol, or a mixture of the two. It is usually prepared by moistening the dried and powdered drug with the appropriate solvent and then packing the mixture into a percolator. When the liquid commences to pass through, the lower orifice of the percolator is closed, and the drug is allowed to macerate (soak) for a specified time, after which percolation is continued until the drug is exhausted. The percolate is then evaporated to a suitable volume and filtered. If water has been employed for the extraction, alcohol must be added to the final product in order to arrest fermentation.

Fig. 3.—SIFTING POWDERED LIQUORICE ROOT WITH THE AID OF A MECHANICAL SIEVE
The tray carrying the sieves is suspended on steel straps and oscillated by means of a power-driven eccentric.

Some liquid extracts are standardised by chemical analysis so that they shall contain a specified percentage of the active principle of the drug. When this is not possible, 1000 millilitres of the extract is made from 1000 grammes of air-dried drug; one fluid part of such a preparation should contain the active principles of one part by weight of the drug and it is known as a "one-in-one" extract.

Fig. 4.—A LARGE SIZE PERCOLATOR USED FOR MAKING LIQUID EXTRACTS AND TINCTURES
This percolator holds 500 lb. of powdered drug.

When making liquid extracts of drugs which are not easily exhausted, the first part of the percolate is reserved and the latter part evaporated to the consistency of a paste, which is then dissolved in the reserved portion and the liquid extract finally adjusted to the required volume. Sometimes this practice is necessary in order to avoid loss of active principles when evaporating the percolate. The first part of the percolate always contains the major portion of the active principle, so that it is sometimes advisable to set this aside and only submit the later portions of the percolate to the action of heat.

A deposit of colouring matter and inert substances always separates from freshly made liquid extracts, and it is therefore neccssary that they should be set aside for some time and then filtered.

Dry Extracts

These preparations find a wide application in the manufacture of pills. They occur as dry free-running powders or granules. The preliminary percolation of the drug is conducted in the same manner as when making liquid extracts, but the evaporation of the liquor is continued until a little taken out of the pan and cooled on a slab is found to be of the desired consistency. While the extract is hot, bubbles of water vapour will rise to the surface, forming a froth which may be removed by skimming ; the extract beneath the scum will be smooth and bright.

When cold, the hard extract is removed, usually by momentarily heating again to soften the outer layer of extract in contact with the pan, and then pulverised.

It is frequently necessary to evaporate the liquors under reduced pressure in order that the temperature shall not rise so high that the active principles are destroyed. For this purpose, vacuum stills with removable heads are employed. When evaporation is conducted under reduced pressure it is often advantageous suddenly to increase the vacuum towards the end of the operation ; this causes the extract to froth vigorously, and when in this condition the last traces of water are readily removed.

Tinctures

A tincture is an alcoholic solution of the soluble matter of a drug. Tinctures often contain the extractive material of more than one drug and they are then termed compound tinctures. They are much weaker preparations than the extracts and find a wide application, since the appropriate dose, being relatively large, is easily measured. The method of preparing tinctures varies with the character of the drug, some being made by maceration, some by percolation and others by diluting liquid extracts or dissolving solid extracts in alcohol of the appropriate strength.

To prepare a tincture by maceration the powdered drug is mixed with the whole of the solvent, and after standing with occasional shaking for a week the liquid is strained off. The solid material which remains, termed the marc, is then pressed and the liquid thus obtained is added to the bulk of the tincture, which is clarified by subsidence or filtration.

If the percolation process is used, the powdered drug is well moistened with the menstruum, and after about 4 hours the mixture is packed in a percolator and more solvent added. When the solvent commences to drop from the percolator the outlet is closed and sufficient menstruum is added to leave a layer above the drug. After macerating thus for 24 hours, percolation is continued until three-fourths of the volume required has been collected. The marc is then transferred to a press (Fig. 5) and the expressed liquid added to the original percolate and the mixture diluted to the required volume and clarified. Since the tissues of vegetable drugs expand when moistened with water or alcohol, it is important that only wetted material should be introduced into the percolator.

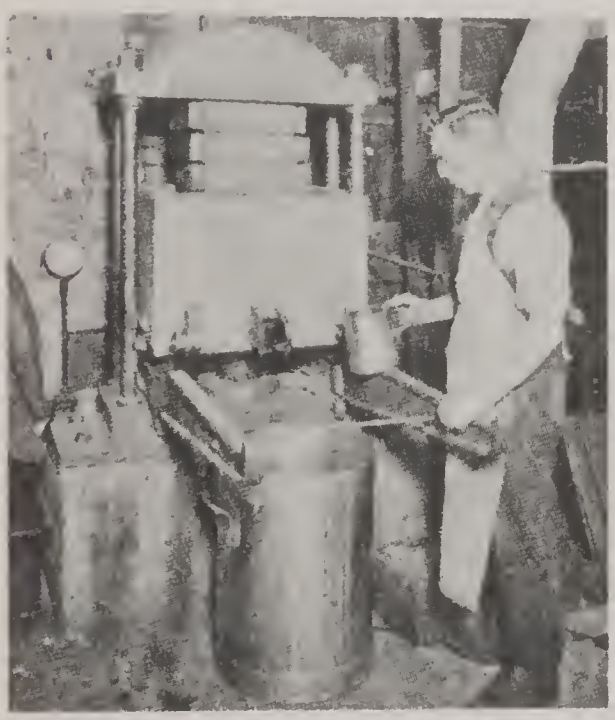


Fig. 5.—HYDRAULIC PRESS FOR RECOVERING RESIDUAL LIQUID FROM MARCS

Fresh Infusions

There are two kinds of infusions, known as fresh and concentrated. A fresh infusion is made by pouring upon the drug cold or boiling water, and at the expiration of 15 or 30 minutes straining off the resulting liquid. The drug may be either powdered or broken into small pieces according to its character. The marc is not pressed after the clear liquid has been strained off. Fresh infusions must be used within 12 hours from the time of their preparation. Special pots, containing a perforated cup to hold the drug, are employed for preparing infusions. This cup is suspended in the upper part of the pot and as the water becomes charged with the extractive matter it sinks and the drug is constantly exposed to fresh portions of less saturated liquid.

Concentrated Infusions

Concentrated infusions, which are used for the extemporaneous preparation of ordinary infusions, are approximately eight times stronger

than their corresponding fresh infusions. The name "infusion" as applied to these preparations is not quite accurate, since they all contain alcohol added as a preservative. They are prepared either by maceration or percolation on principles similar to those adopted in making liquid extracts.

Decoctions

These preparations are made by mixing the drug in coarse powder or small pieces with cold water, heating the mixture until the water boils, and allowing to simmer gently for a prescribed time varying from 10 to 30 minutes. After cooling, the liquid is strained and diluted to the desired volume.

Other Pharmaceutical Preparations

There are other pharmaceutical preparations especially applicable to individual drugs which will be mentioned in the more detailed account which is to follow.

PHARMACOPŒIAS

It will readily be understood that consignments of drugs of plant origin are liable to vary considerably in quality. They are subject to the influence of climatic conditions and the quality of the soil in which they are grown. Furthermore, there is always the possibility of spurious material, similar in outward appearance, being offered for sale. These contingencies have to be carefully guarded against by manufacturing chemists dealing with these commodities. Again, it is most important that physicians should be assured that the galenicals which they prescribe shall be

Fig. 6.—Determination of the ash for judging quality of vegetable drugs (1)
A quantity of an air-dried drug is first weighed.

prepared to known standards of strength. This uniformity is achieved by the publication in all civilised countries of pharmacopœias. In these books, standards are defined as to the quality of raw drugs and the strength of galenicals. As certain drugs become obsolete and new remedies are discovered, the pharmacopœias become out of date, and it is therefore necessary to issue fresh standards to suit the changed conditions.

The present British Pharmacopœia was published under the direction of the General Medical Council and is dated 1932. Great care is essential in preparing a book of this character, since it is necessary to consult the highest authorities on medicine, pharmacology, pharmacognosy, pharmacy and chemistry. The British Pharmacopœia 1932 occupies 713 closely printed pages and was produced by the Pharmacopœia Commission, consisting of seven members and a secretary, with the assistance of six sub-committees. Wherever possible, definite standards of quality are fixed and methods of chemical analysis are described. Every test and every statement has been the subject of careful discussion. In order to keep abreast of recent advances in medicine, pharmacy and chemistry and to meet changing conditions of supply five Addenda to the Pharmacopœia have been published.

Fig. 7.—Determination of the ash (2)
The ash is burnt over a bunsen burner until all the organic material has been completely burnt away.

GENERAL TESTS FOR CRUDE DRUGS

In judging the quality of vegetable drugs, it is often useful to apply certain empirical tests, such as the determination of the percentage of residue left after incineration (the ash), and the percentage of extractive material yielded to alcohol or water. General appearance and botanical characteristics must also be considered, and in the case of powdered drugs of all kinds, a microscopical examination of the histological elements is important in order to detect possible adulteration with foreign material; this work demands considerable patience

and involves a detailed knowledge of plant histology.

Determination of the Ash

The ash is determined by incinerating a weighed quantity of the air-dried drug in a tared dish of platinum or silica until all the organic material has been completely burnt away. After weighing the residue it is often useful to determine the proportion of the ash which is insoluble in dilute hydrochloric acid. The acid is added to the ash and. after boiling for 5 minutes, any insoluble material is collected by filtering through an "ashless" filter paper. After washing with hot water the filter paper containing the insoluble material is burnt away in the same dish, which is then again weighed.

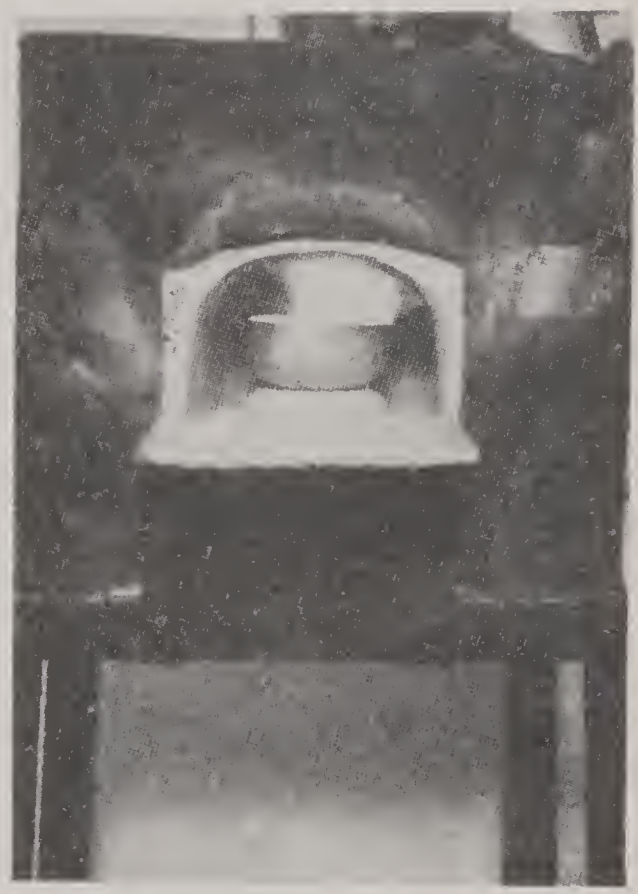


Fig. 8.—Determination of the ash (3) By ashing in an electric muffle furnace the ash is unaffected by any gas vapours.

Determination of Soluble Extractive

The soluble extractive material of crude drugs should be determined under standardised conditions. The British Pharmacopœia directs that 5 gm. of the air-dried drug in coarse powder (a powder of which all the particles pass through a No. 10 sieve and not more than 40 per cent. through a No. 44 sieve) should be macerated in a closed flask for 24 hours with 100 ml. of alcohol of the strength specified for the particular drug being tested. The mixture is then filtered, and 25 ml. is evaporated to dryness in a tared shallow dish, and the residue, dried at 100° C., is weighed. If a water-soluble extractive determination is to be made, chloroform water must be used to inhibit the possibility of fermentation taking place. Chloroform water is made by dissolving 2·5 ml. of chloroform in sufficient water to make a total volume of 1 litre ; this represents an approximately saturated solution of chloroform in water.

The determination of the concentration of active ingredients present in drugs and their galenicals usually involves the application of complicated analytical procedures. As some understanding of these methods affords valuable instruction to the student a considerable space is devoted to their discussion in the descriptions of the individual drugs.

Chapter II

OPIUM

IN one of his dissertations, Thomas Sydenham, the great seventeenth-century physician and founder of the modern clinical method, remarked that " without opium I would not care to practise medicine." This observation would doubtless be endorsed by most physicians of to-day. Opium, when considered in association with the use of its isolated alkaloids, is probably the most important drug known to mankind.

The drug consists of the dried latex obtained from the unripe capsule, or fruit, of *Papaver somniferum*, a species of poppy bearing white or bluish-purple flowers. The capsule of this plant is usually 2 to 5 cm. in diameter and therefore much larger than that of the European red poppy. Opium is produced commercially in Asia Minor, European Turkey, Bulgaria, Jugoslavia, Persia, India and China. The mode of production and appearance of the drug vary with the country of origin. Most of that used for medicinal purposes in this country comes from Asia Minor, India and Persia.

Fig. 1.—TURKISH POPPY CAPSULES AND IMPLEMENTS

The capsules are shown after being incised : in the centre is a seven-bladed knife which is used for making the incisions and, on the right, a copper tray for collecting the latex.

Production of Turkish Opium

The opium poppy requires a moist soil and careful attention, and in Asia Minor is mostly cultivated by peasant proprietors. The seed is usually sown in December and after the fall of the petals in June the plants are ready for incision, which is accomplished by cutting each capsule transversely with a 7-bladed knife so that the juice slowly exudes during the night. In the morning the partially dried latex is transferred to poppy leaves and allowed to dry further for a few days in a

shady place. At this stage it used to be sold to dealers who compressed it into cakes of variable size, wrapped it in poppy leaves, covered each cake with rumex fruit, and packed them into bags. This practice has been superseded since, in 1935, the Turkish Government took over the marketing of opium as a State monopoly, and the "druggist's" quality, which used to occur in the form of irregular-sized balls of varying consistency, is now exported in uniform masses. In the Turkish Government factory a bulk of the collected opium is made, put through some form of mill and then pressed into moulds so that the material is homogeneous throughout whole consignments.

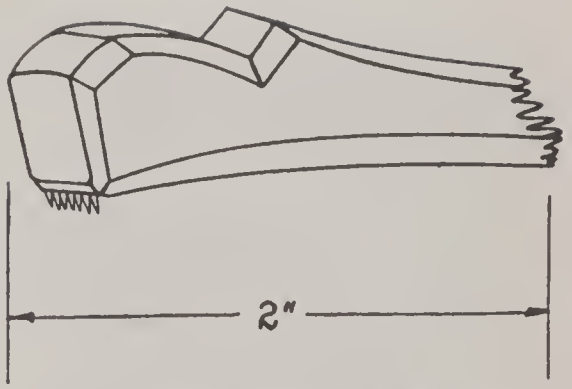


Fig. 2.—TURKISH SEVEN-BLADED KNIFE

This diagram shows the details of the seven small knife blades, the shaft of the instrument being omitted.

The pieces, of which forty are packed in a metal-lined case, are approximately cylindrical in shape but somewhat flattened where they have been pressed together, thus causing their transverse section to assume an elliptical shape. They are approximately 13 cm. in diameter and 9·5 cm. thick and of a mottled pale yellowish-brown colour, due to the

Fig. 3.—TURKISH GOVERNMENT MONOPOLY OPIUM

The size of the "masses" is indicated by the foot rule set in front. Note the hole which has been bored in the uppermost piece for the purpose of sampling. On three of the other "masses" the official label can be seen.

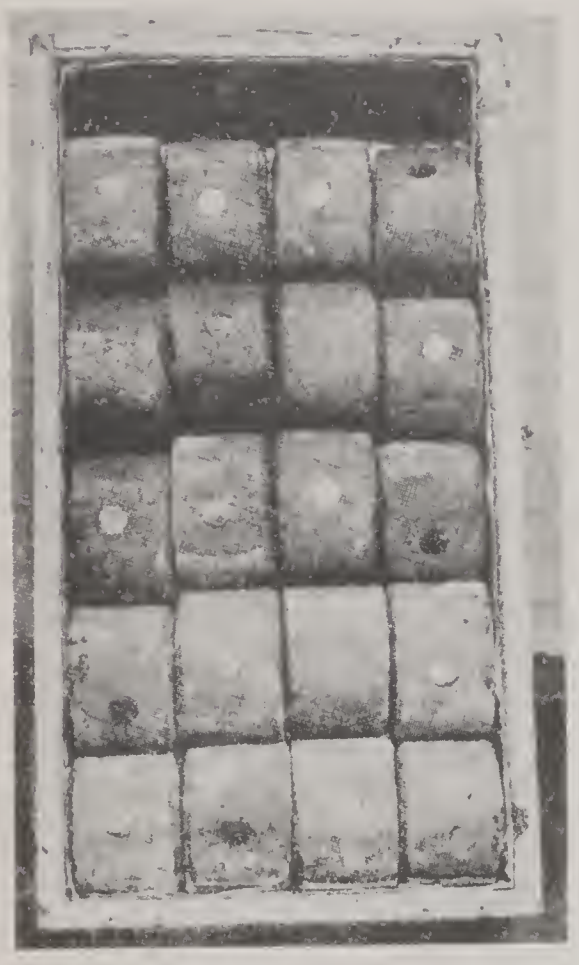


Fig. 4.—Turkish government monopoly opium

An original metal-lined case packed with two layers each of twenty pieces.

coarsely powdered leaf which adheres to the surface. Each piece, which weighs 2 kg., has affixed to it a paper label in black and gold relief bearing the letters IMU inside a star and crescent device. The cut surface is chocolate-brown in colour, soft, moist and apparently homogeneous.

Production of Jugoslavian Opium

The poppy capsules are incised by the use of a knife with a small curved and pointed blade in the manner shown in the centre of Fig. 5. The inspissated latex is collected in metal containers and sent to the Government factory at Belgrade, where it is milled and made into flat oblong cakes 1·5 to 2·5 cm. thick, 18 to 20 cm. long and 6 to 7·5 cm. wide. The cakes, which have rounded ends, are placed on wire-netting to dry and then packed with rumex fruits into cases holding about 80 kg. As in Turkey, so also in Jugoslavia, all opium is produced under strict Government supervision.

Production of Persian Opium

The cultivation centres round Ispahan. Contrary to the practice of other countries pale-coloured material is the most esteemed; consequently the capsules are cut during the evening and the inspissated juice is collected just before sunrise, since daylight rapidly discolours the exuded latex. In order to exclude the light of advancing day, the masses of drying juice are conveyed from the plantations in copper vessels instead of on poppy leaves. The juice is dried in sheds until its weight is reduced by about one-fifth and then mixed with 20 per cent. or more of sarcocolla gum, or else with grape juice, the product gently boiled with constant stirring, and the resulting paste moulded into bricks, each of which is wrapped in red paper. It is shipped from Bushire or Bundar Abbas.

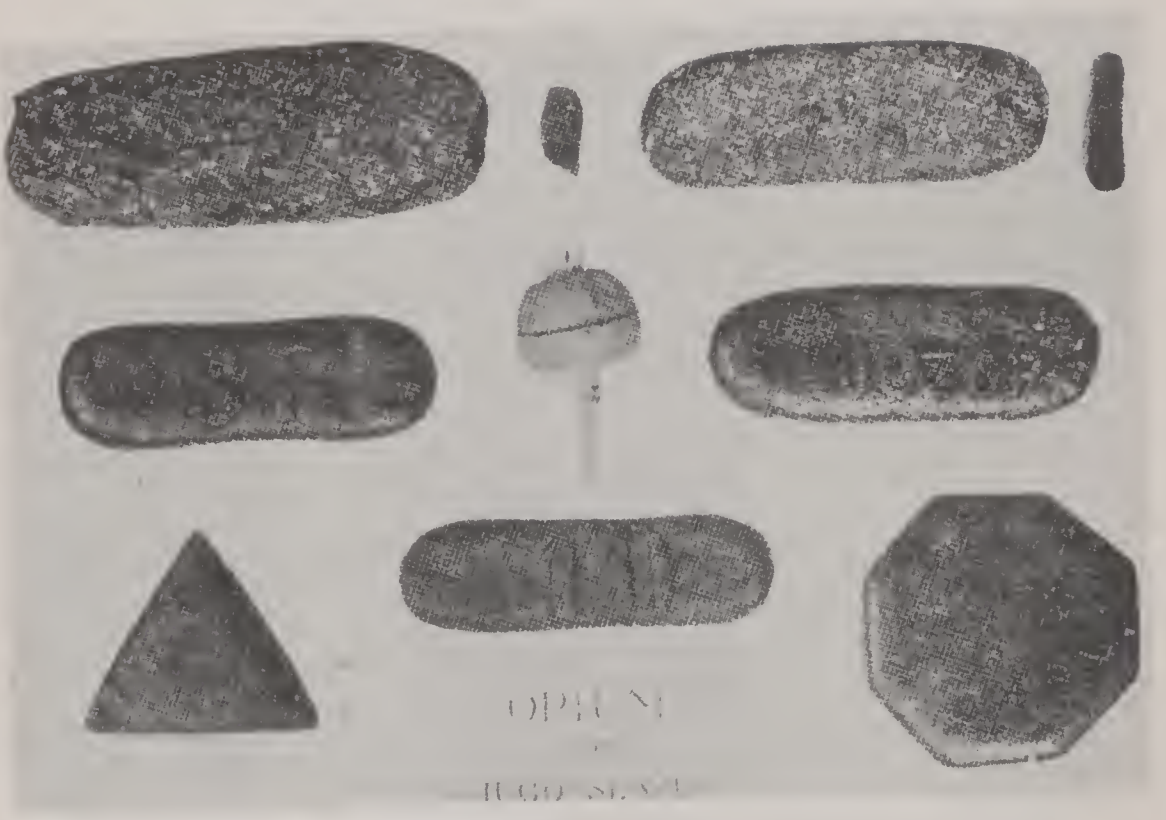


Fig. 5.—Seven pieces of Jugoslavian opium

The two in the top row are covered with roughly powdered poppy leaves and were the type originally exported. Latterly, the poppy leaf coating has been discontinued as seen in the pieces depicted in the central row, marked ST (indicating the place of origin, Stroumitsa) and Juzop (which is the telegraphic address of the Jugoslavian bureau) respectively. The triangular and octagonal pieces are never exported. The small cake marked 10 has been adjusted for morphine content by mixing with sugar of milk. (From an account by T. E. Wallis, *Pharmaceutical Journal*, 9th December, 1939.)

The material has a homogeneous texture and resembles chocolate in appearance, although it does not crumble when cut with a knife. It is harder and more constant in quality than the opium of other countries, although generally the proportion of physiologically active constituents is not quite so high.

Production of Indian Opium

Opium is mainly produced in the central districts of the Ganges, including Behar, Benares and Patna, and the tablelands of Malwa which lie to the north-east of Bombay. The entire production is controlled by the Indian Government. After collection, the latex is dried until the moisture content is reduced to about 10 per cent., made into cakes or tablets varying in size and shape according to the district of origin and then wrapped in white paper. While Indian opium is not so suitable for the preparation of galenicals as the drug derived from Asia Minor or

Fig. 6.—UNDER-SURFACES OF THREE CAKES OF JUGOSLAVIAN OPIUM

The impression left by the wire netting of the shelves on which the cakes are dried is clearly seen in the right-hand specimen.

Persia, it is particularly favoured by manufacturers for the production of morphine and codeine.

Chemistry of Opium

Twenty-five alkaloids have been isolated from opium. Of these morphine ($C_{17}H_{19}O_3N$) is the most important and generally occurs to the extent of 10 to 13 per cent. in " druggist's " quality Turkey opium, while the Persian drug usually contains from 9 to 11 per cent. Codeine, which is morphine methyl ether ($C_{18}H_{21}O_3N$), ranks second in importance to morphine and is present to the extent of 0·3 to 1·9 per cent. With the possible exception of papaverine, the other alkaloids of opium are not of medicinal importance, although salts of narcotine, narceine, and thebaine are very occasionally used. For the most part the alkaloids occur in the drug combined as salts with meconic and sulphuric acids. Other constituents include mucilage, sugar, wax, and salts of calcium, magnesium and potassium.

Therapeutic Uses of Opium

The physiological action of opium is essentially hypnotic and is mainly due to the morphine which it contains. Most of the other alkaloids have similar, though not identical, therapeutic properties but are not present in sufficient quantity to render the action of opium widely different from that of its principal constituent. The drug depresses the sensory nerve cells in the cerebrum without affecting the motor nerves. The sedative action first diminishes the normal self-control and, in small doses, results in an apparent stimulation consequent on the removal of the restraint which ordinarily governs behaviour. In larger doses sensations of pain are eradicated and it is the best drug known for the treatment of sleeplessness due to painful disease ; for this purpose salts of morphine itself are usually employed.

Apart from its narcotic action opium augments the secretion of perspiration by dilating the skin vessels and thus affords a remedy for catarrhal disorders. In respiratory diseases opium, morphine or codeine are used to check cough and dyspnœa ; for this purpose it is often combined with expectorants such as ipecacuanha.

Pharmacy of Opium

The number of preparations containing opium is so large that space will not allow of their individual description, and only the more important galenicals will be discussed. In Table II the general character of a large number of opium preparations is indicated.

TABLE II—THE PRINCIPAL PREPARATIONS CONTAINING OPIUM

Name	*Per Cent. Morphine*	*Solvent or Diluent*	*Main Constituents Other Than Opium*	*Remarks*
*Dry extract of opium	20	Calcium phosphate	—	Used for pills.
*Powdered opium ..	10	Lactose ..	—	Used for official mixed powders and suppositories.
Compound pill of soap	About 2	Syrup of liquid glucose	Hard soap ..	—
Pill of lead with opium	About 1·2	Syrup of liquid glucose	Lead acetate ..	Remedy for diarrhœa.
*Tincture of opium..	1	Alcohol (about 45 per cent.)	—	—
*Powder of ipecacuanha and opium	1	Lactose or potassium sulphate	Ipecacuanha ..	Diaphoretic for colds, etc. Called Dover's powder.

TABLE II—THE PRINCIPAL PREPARATIONS CONTAINING OPIUM—*continued.*

Name	*Per Cent. Morphine*	*Solvent or Diluent*	*Main Constituents Other Than Opium*	*Remarks*
Compound powder of opium	1	—	Black pepper, ginger, caraway	—
Sedative solution of opium	1	Dilute alcohol and sherry	—	Used in place of the tincture.
Liquid extract of opium	0·75	Alcohol (about 18 per cent.)	—	—
Gall and opium ointment	0·75	Benzoinated lard	Gall	—
Compound powder of kino	0·5	—	Kino, cinnamon	Remedy for diarrhœa.
Pill of ipecacuanha with squill	About 0·5	Syrup of liquid glucose	Ipecacuanha, squill, ammoniacum	—
Tincture of opium with saffron	About 0·5	Detannated sherry	Saffron, cinnamon, cloves	Called Sydenham's laudanum.
†Concentrated camphorated tincture of opium	0·4	Alcohol (about 60 per cent.)	Camphor, benzoic acid, oil of anise	—
*Aromatic powder of chalk with opium	0·25	Sucrose ..	Chalk, cinnamon, nutmeg, clove, cardamom	Prescribed for treatment of diarrhœa.
Ammoniated tincture of opium	0·1	Alcohol (about 70 per cent.)	Ammonia, benzoic acid, oil of anise	—
*Camphorated tincture of opium	0·05	Alcohol (about 56 per cent.)	Camphor, benzoic acid, oil of anise	Called paregoric.
*Suppository of lead with opium	1/10 grain in each	Oil of theobroma	Lead acetate ..	Used for hæmorrhoids.

* These preparations are included in the British Pharmacopœia 1932.
† Included in the 5th Addendum, 1942, to the British Pharmacopœia 932.

Tincture of Opium, or Laudanum

This is standardised to contain 1 per cent. of anhydrous morphine, and is prepared by adding boiling water to the sliced drug, setting aside for 6 hours, adding an equal volume of 90 per cent. alcohol and, after allowing the mixture to stand for 24 hours, straining and pressing the marc. After mixing the liquids the preparation is kept for 24 hours,

filtered, and assayed for its morphine content. The strength of the tincture is then finally adjusted by adding a mixture of equal volumes of 90 per cent. alcohol and distilled water. The tincture is specially used in preference to solutions of morphine to allay gastric and abdominal pain in diarrhœa and dysentery, and wherever delayed absorption is desirable.

Paregoric

This preparation, also known as compound tincture of camphor or camphorated tincture of opium, is prepared by diluting 5 vols. of tincture of opium to 100 vols. with a solution of benzoic acid, camphor and oil of anise in 60 per cent. alcohol. The finished product contains 0·05 per cent. of morphine and 0·3 per cent. of camphor. It is extensively used in the treatment of cough.

Dry Extract of Opium

The dry extract is mainly employed in the preparation of pills. It is prepared by treating the sliced opium with boiling water and, after 6 hours, straining and pressing the marc. The liquids are mixed and the product assayed for total solids and for morphine content. The preparation is then evaporated to dryness after adding the necessary amount of calcium phosphate to produce a dry extract containing 20 per cent. of morphine.

Dover's Powder

Frequently termed compound powder of ipecacuanha, this preparation contains 10 per cent. of opium, together with ipecacuanha and lactose. Thomas Dover, the originator of this valuable diaphoretic, was at one time a buccaneer and in 1709, as captain of the privateer *Duke*, rescued Alexander Selkirk, who had lived alone on an island for over four years. Returning with his ship full of treasure in 1710, Dover set up in medical practice with no other qualification apart from having once been a servant of Thomas Sydenham.

Assay of Opium

Opium is almost invariably evaluated on its content of morphine and a very large number of processes for effecting this have been proposed. Morphine, although responding to most of the tests characteristic of alkaloids, differs from the majority of these bodies in being almost insoluble in chloroform, ether or petroleum spirit. The methods of morphinometric assay do not follow on the same lines as the processes for assay generally adopted for other alkaloidal drugs. The following method involves the principle most usually favoured in this country :—

Eight gm. of a carefully prepared representative sample of the bate-

under test is triturated in a mortar with 2 gm. of calcium hydroxide and 20 ml. of water until a uniform mixture results, when an additional 60 ml. of water is added and the mixture stirred occasionally during half an hour. The mixture is filtered through a pleated paper and 51 ml. of the clear filtrate, containing the morphine as water-soluble calcium morphinate, is transferred to a flask and mixed with 5 ml. of 90 per cent. alcohol, 25 ml. of ether, and 2 gm. of ammonium chloride. The ammonium salt reacts with the calcium morphinate liberating the morphine alkaloid which settles out as a precipitate, the ether dissolving all other alkaloidal material. After vigorous shaking during half an hour the flask is set aside overnight, the morphine collected in a Gooch crucible and the flask and precipitate washed repeatedly with morphinated water (a saturated solution of morphine in water containing 0·25 per cent. by volume of chloroform). The crucible is transferred to a beaker containing 20 ml. of decinormal sulphuric acid and about 100 ml. of water, the liquid is boiled for a few minutes until all the morphine has dissolved and, after allowing to cool, the excess of acid is titrated with decinormal sodium hydroxide using methyl red as indicator. Each ml. of decinormal acid is equivalent to 0·02852 gm. of morphine. To the amount indicated by the titration 0·051 gm. is added to correct for the loss of morphine due to its solubility.

Assay of Tincture of Opium

Forty ml. of the sample is evaporated until its volume is reduced to about 10 ml., 1 gm. of calcium hydroxide is added and, after mixing, the liquid is diluted to 41 ml. with water. After half an hour the mixture is filtered, 25 ml. of the filtrate is transferred to a flask and treated with 2·5 ml. of 90 per cent. alcohol, 15 ml. of ether and 1 gm. of ammonium chloride. The process is then the same as for the assay of opium itself excepting that 0·025 gm. is added to the result to compensate for the loss of morphine due to its solubility.

MORPHINE

On a manufacturing scale morphine may be isolated by triturating opium with sufficient calcium chloride solution to form a thin paste, and extracting with hot water. This converts the morphine and other alkaloids into their respective hydrochlorides, while the acids with which they were combined in the drug are precipitated as insoluble calcium meconate and calcium sulphate. The insoluble matter is separated by filtration, and, to prevent oxidation, sodium sulphite is added to the filtrate, which is then concentrated *in vacuo* to the consistency of a thin syrup. Sodium acetate solution is added in order to precipitate narcotine and papaverine which are removed by filtration.

A small proportion of alcohol is added to the filtrate, the morphine is precipitated by the addition of lime in the presence of ammonium chloride, and, after allowing to stand for some time, the morphine is filtered off. Codeine may be extracted from the filtrate by shaking with benzene.

The crude morphine is washed with benzene to remove traces of codeine, then mixed with boiling water and neutralised with hydrochloric acid, atmospheric oxidation being prevented by covering with a layer of petroleum. Morphine hydrochloride crystallises out on cooling and is purified by recrystallisation from water. If desired, the base may be obtained by precipitating an aqueous solution of the salt with ammonia.

Properties of Morphine and its Salts

Pure morphine occurs in odourless white needle-shaped crystals, or as a white crystalline powder almost insoluble in water and common organic solvents. The hydrochloride is the most important salt and when pure appears as colourless glistening needles or as a crystalline powder soluble in water.

Tests for Morphine

A simple test consists in adding a drop of nitric acid to solid morphine or one of its salts, when an orange-red colour is produced. Another reaction which is very sensitive depends on its property of reducing ferricyanide to ferrocyanide. The test is conducted by adding to the liquid containing a trace of morphine a dilute and freshly prepared solution of potassium ferricyanide (free from ferrocyanide) to which a little ferric chloride has been added ; the presence of morphine is revealed by the development of a bluish-green colour.

Another useful reaction for morphine is conducted by adding a small crystal of sodium nitrite to an acid solution of the alkaloid followed by an excess of ammonia, when a brownish-yellow colour is produced. This test may be used for the colorimetric determination of morphine and is employed in the official process for the assay of camphorated tincture of opium. Codeine does not give the reaction, and morphine, present as impurity in salts of codeine, may be detected and determined by this method.

Synthetic Derivatives of Morphine

Apomorphine ($C_{17}H_{17}O_2N$) is derived from morphine by the abstraction of the elements of water. The hydrochloride is used as a powerful emetic.

Diamorphine, diacetylmorphine, or heroin is formed by the action of acetic anhydride on morphine. Its physiological action resembles that of morphine but its narcotic effect is weaker. It is particularly useful for allaying irritant coughs due to asthma and bronchitis.

Many other synthetic derivatives of morphine are in use for which various special advantages are claimed. In general, however, their therapeutic effects are similar to those of morphine and they do not call for special comment.

Pharmacy of the Isolated Alkaloids

A large number of galenicals containing the isolated alkaloids of opium or their synthetic derivatives are in use and the main characteristics of the more important of these are summarised in Table III.

TABLE III—THE PRINCIPAL PREPARATIONS OF MORPHINE AND ITS DERIVATIVES

Name	*Per cent. Morphine Hydrochloride*	*Per cent. Codeine*	*Per cent. Diamorphine Hydrochloride*	*Per cent. Apomorphine Hydrochloride*	*Other Constituents*	*Remarks*
Injection of morphine	2·5	—	—	—	Distilled water preserved with chlorocresol	Administered subcutaneously. Dose 3–10 minims.
*Solution of morphine hydrochloride	1	—	—	—	Hydrochloric acid 0·2 per cent., dilute alcohol	—
Solution of morphine acetate	1 (acetate)	—	—	—	Dilute alcohol ..	—
Solution of morphine tartrate	1 (tartrate)	—	—	—	Dilute alcohol ..	Used for injection.
Bismuth and morphine insufflation	0·4	—	—	—	Bismuth subnitrate, powdered acacia	Ferrier's snuff for nasal disorders.
Compound tincture of chloroform and morphine	0·229	—	—	—	Chloroform, ether, hydrocyanic acid, liquorice, peppermint, etc.	A form of chlorodyne.
Tincture of chloroform and morphine, B.P. 1885	0·2	—	—	—	Chloroform, ether, etc. (see text)	A favoured form of chlorodyne.
Compound chloroform mixture	0·09	—	—	—	Hydrobromic acid, chloroform, cherry-laurel water, syrup	—
*Morphine suppository	¼ grain in each	—	—	—	Oil of theobroma	—
Morphine lozenge	$\frac{1}{30}$ grain in each	—	—	—	Sucrose, acacia, tolu	—
*Morphine and ipecacuanha lozenge	$\frac{1}{32}$ grain in each	—	—	—	Ipecacuanha, sucrose, acacia, tolu	See page 73.
Chlorodyne lozenge	$\frac{1}{60}$ grain in each	—	—	—	Chloroform, ether, peppermint, capsicum, sucrose, etc.	Valuable for coughs.

TABLE III—THE PRINCIPAL PREPARATIONS OF MORPHINE AND ITS DERIVATIVES—*continued*

Name	*Per cent. Morphine Hydrochloride*	*Per cent. Codeine*	*Per cent. Diamorphine Hydrochloride*	*Per cent. Apomorphine Hydrochloride*	*Other Constituents*	*Remarks*
Syrup of codeine phosphate	—	0·5 (phosphate)	—	—	Syrup, tragacanth, chloroform	Used for making linctus of codeine.
Linctus of codeine	—	0·25 (phosphate)	—	—	Syrup, oil of anise, quillaia, tragacanth	For coughs and throat disorders.
Codeine jelly ..	—	0·2	—	—	Citric acid, glycerin, gelatin, etc.	Codeine does not induce drug habit.
Compound tablets of acetanilide with codeine	—	$\frac{1}{6}$ grain in each	—	—	Acetanilide, caffeine, sodium bicarbonate	A strong sedative.
Linctus of diamorphine	—	—	0·1	—	Hyoscyamus, chloroform, tolu, syrup of wild cherry, etc.	Remedy for coughs and bronchial affections.
Compound elixir of diamorphine and pine	—	—	0·05	—	Oil of pumilio pine, terpin hydrate, sucrose, etc.	Ditto.
Camphorated linctus of diamorphine	—	—	0·046	—	Camphor, benzoic acid, ipecacuanha, squill, etc.	Ditto.
Linctus of diamorphine with ipecacuanha	—	—	0·046	—	Ipecacuanha, hyoscyamus, chloroform, syrup of wild cherry, etc.	Antispasmodic and expectorant.
Linctus of diamorphine and squill	—	—	0·046	—	Squill, sodium antimonyl tartrate, senega, etc.	Antispasmodic.
Elixir of diamorphine and terpin with apomorphine	—	—	0·046	0·057	Terpin hydrate, glycerin, syrup of wild cherry, etc.	Remedy for coughs and bronchial affections.
Linctus of diamorphine and thyme	—	—	0·046	0·057	Liquid extract of thyme, tolu, glycerin	Useful for whooping cough.
Compound diamorphine and pine pastilles	—	—	$\frac{1}{48}$ grain in each	—	Oil of pumilio pine, terpin hydrate, gelatin, glycerin	—
Syrup of apomorphine	—	—	—	0·05	Hydrochloric acid, alcohol, syrup	Used as an expectorant.

* These preparations are included in the British Pharmacopœia 1932.

Chlorodyne

A notable preparation which owes its action mainly to the morphine it contains is chlorodyne. Several formulæ for this have been proposed, one of which consists in mixing together 6 parts of chloroform, 3 parts of tincture of Indian hemp, 1·5 parts of tincture of capsicum, 22 parts of glycerin, 1 part of spirit of peppermint, with 12·5 parts of alcohol ; 0·5 part of morphine hydrochloride is dissolved in this liquid and 12 parts of liquid extract of liquorice, 12 parts of mucilage of gum acacia and 25 parts of treacle are added, and the whole made up to 100 parts with more alcohol. The British Pharmacopœia of 1885 included a tincture of chloroform and morphine which is still considered by many physicians to be the best available form of chlorodyne. It consists of chloroform, 12·5 ; ether, 3·125 ; alcohol, 12·5 ; morphine hydrochloride, 0·2 ; diluted hydrocyanic acid, 6·25 ; oil of peppermint, 0·1 ; liquid extract of liquorice, 12·5 ; treacle, 12·5 ; and syrup sufficient to produce 100. Both preparations are effective remedies for diarrhœa, colic, flatulence and coughs.

Drug Habit and Opium

The administration of opium, by virtue of the morphine which it contains, is liable to lead to a craving for the drug. For this reason the sale and distribution of opium and morphine, with some of its artificial derivatives, is controlled by the Regulations made under the Dangerous Drugs Acts. Small doses of opium engender a greatly augmented sense of self-confidence and it is recorded that John Hunter, the famous surgeon, who disliked public speaking, used to prepare himself for such ordeals by taking 30 drops of laudanum.

An extraordinary immunity to the drug results after long indulgence so that large quantities are taken in order to satisfy the subject. Thomas De Quincey consumed 9 fluid ounces of the tincture per day before he finally conquered the habit. De Quincey's description of the sensations which precede the sleep due to a dose of opium will form an appropriate conclusion to this account of the most remarkable vegetable drug known to man. "Here were the hopes which blossom in the paths of life, reconciled with the peace which is in the grave ; motion of the intellect as unwearied as the heavens, yet for all anxieties a halcyon calm ; tranquillity that seemed no product of inertia, but as if resulting from mighty and equal antagonisms ; infinite activities, infinite repose."

Chapter III

THE SOLANACEOUS GROUP OF ALKALOIDAL DRUGS

THE plants which contain alkaloids constitute the most important series of drugs of vegetable origin. The general chemical character of the alkaloids has already been described in the first chapter, and it will only be necessary to repeat here that they are all nitrogenous organic bases, most of which are sparingly soluble in water but dissolve readily in chloroform or ether. When combined with acids they form salts which are usually much more soluble in water than in organic solvents. If a strong alkali, such as ammonia or sodium hydroxide, is added to an aqueous solution of an alkaloidal salt the alkaloid itself is liberated and often forms a precipitate. The chemical processes used for the extraction of alkaloids from the plant tissues depend upon these properties.

Many chemicals produce precipitates when added to aqueous solutions of alkaloidal salts, among which may be specially mentioned picric acid, tannic acid, Mayer's reagent (potassio-mercuric iodide) and Dragendorff's reagent (potassium bismuth iodide). Some of these tests are very delicate and by making a judicious choice of the reagents available it is possible to detect and identify the nature of extremely minute quantities of alkaloidal material. In addition, there are various characteristic colour reactions which will be mentioned in the detailed descriptions to follow.

The drugs to be described in this chapter all belong to the Natural Order Solanaceæ and are characterised by containing the same group of

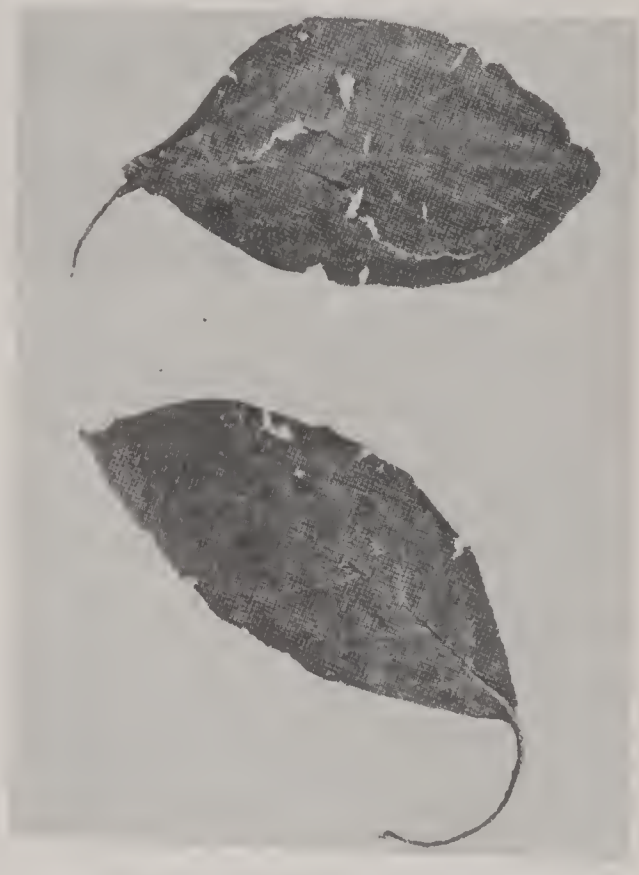


Fig. 1.—BELLADONNA LEAVES

This shows two dried leaves which have been soaked in water and then mounted on a card.

alkaloids. As, however, the proportions in which the alkaloids occur vary considerably, the therapeutic applications of the drugs which constitute the group are not identical.

BELLADONNA

Both the leaf and the root of the deadly nightshade (*Atropa Belladonna*) are extensively employed in pharmacy. This tall, branching perennial herb is widely distributed throughout central and southern Europe, and grows wild in southern England. It is cultivated for medicinal purposes in Bedfordshire, Hertfordshire, Suffolk and elsewhere. The ovate leaves vary from 8 to 20 cm. in length and taper to an acute point. They are almost free from hairs and the underside exhibits a prominent midrib, while the lateral veins do not quite meet the margin, which is entire. For official purposes the leaves should be gathered when the plant is in flower, and then dried.

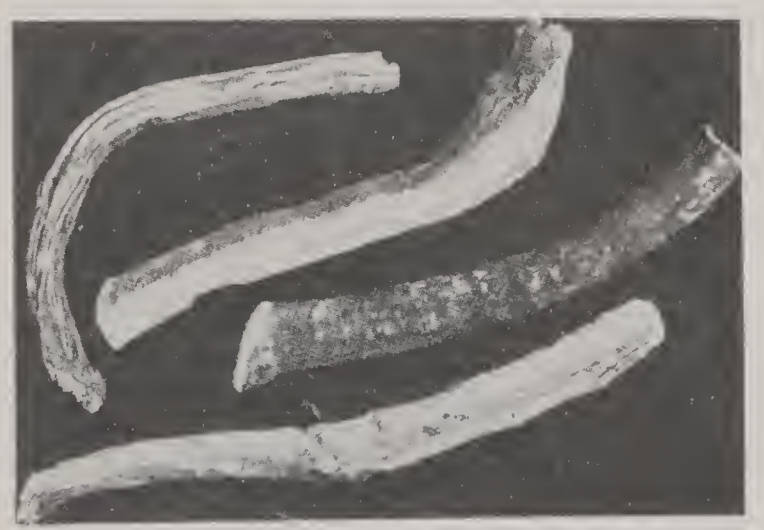


Fig. 2.—Belladonna root

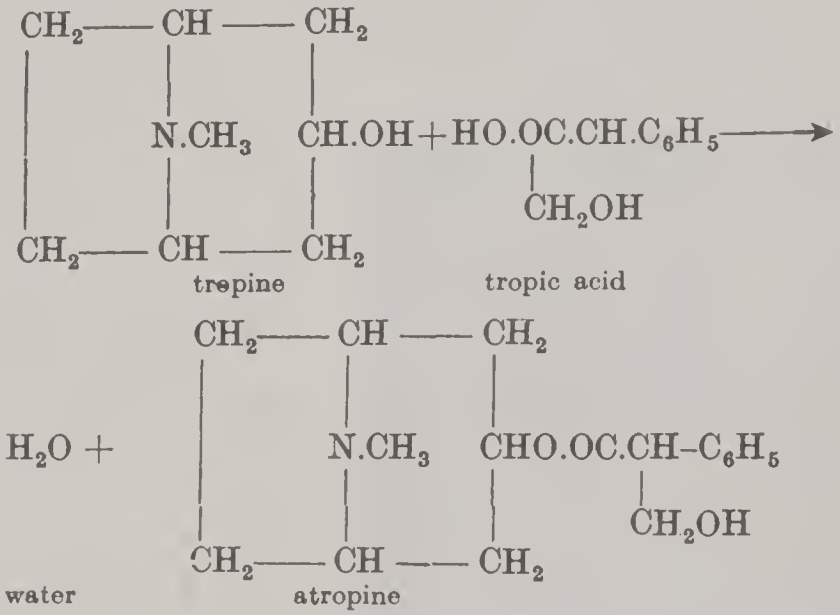
These pieces are about 15 cm. long. It will be noted that one piece has been cut longitudinally, a practice which facilitates the drying process.

Dried belladonna root occurs in commerce in pieces averaging about 15 cm. in length and up to 4 cm. in diameter at the crown. Externally, the root is longitudinally wrinkled and is pale greyish-brown in colour, while the central woody portion is nearly white. It should be collected in the autumn and taken from plants about three or four years old.

Chemistry of Belladonna

The most important constituent of the growing plant is the alkaloid hyoscyamine which is present in the form of a salt and not as the free base. Good specimens of the dried drug, either root or leaf, may contain from 0·4 to 0·8 per cent. of total alkaloid, consisting chiefly of hyoscyamine. Hyoscyamine is optically active but during the process of extraction from the plant tissues it tends to change into the optically inactive isomeride which is called atropine. The empirical formula for atropine (and hyoscyamine) is $C_{17}H_{23}NO_3$ and it may be regarded as a condensation product resulting from the combination of tropic acid and the complex basic alcohol tropine.

The structure of the molecule is best illustrated by the graphical equation :—



It is stated that besides hyoscyamine, belladonna contains traces of other alkaloids, notably hyoscine and belladonnine, but the amount of these present is very small.

Assay of Belladonna

The chemical evaluation of this drug consists in making a determination of the total alkaloids present. With some exceptions the assay of alkaloidal drugs follows the same general scheme, which is well illustrated by the method adopted for the solanaceous group. The following process is applicable to both the leaf and root of belladonna.

A weighed quantity (10 gm.) of the finely powdered drug is introduced into a dry flask, macerated with a mixture of ether and alcohol for 10 minutes and the mixture then rendered alkaline by adding a little dilute ammonia. This treatment liberates the alkaloidal base from its salt combination. After allowing to stand with frequent shaking for 1 hour, the contents of the flask are transferred to a small percolator (Fig. 3) and the drug is percolated, first with the ether-alcohol mixture and then with ether alone, until the alkaloids are extracted.

In order to ascertain when complete extraction has taken place, a few drops of the solvent from the percolator are collected on a watch glass and the solvent is evaporated, any residue left is treated with dilute hydrochloric acid and a drop or two of Mayer's reagent, when, if extraction is not complete, a cream-coloured precipitate or turbidity, indicative of the presence of alkaloid, will appear, but otherwise the liquid will remain clear. Owing to the tendency for the alkaloids to hydrolyse during extraction, the percolation should not occupy more than 3 hours.

The percolate is now transferred to a separating funnel and shaken with an excess of dilute hydrochloric acid ; after separation has occurred the lower acid aqueous layer is drawn off into another separating funnel and the ethereal layer extracted twice or thrice more with small portions of dilute acid mixed with a little alcohol. In this way, the alkaloids are transferred from the ether to the aqueous acid liquid. The alcohol is added to prevent the formation of troublesome emulsions.

Fig. 3.—Assay of belladonna

Percolating with ether-alcohol mixture in order to extract the alkaloid from the powdered drug. The percolator is lightly plugged with cotton wool before the drug is introduced. In this way the percolate is filtered as it passes into the flask.

The acid solution of the alkaloids is now freed from traces of chlorophyll and extractive matter by shaking with a little chloroform, allowing to separate, and drawing off the chloroformic liquid into another separating funnel and there shaking with a little dilute acid in order to remove any trace of alkaloid which may have passed into the chloroform.

After separation, the chloroform is rejected. This treatment with chloroform is repeated twice, the same acid being used to wash the chloroform. When the last washed chloroform has been rejected the acid used for the washing is added to the bulk of the acid liquid and the whole is rendered alkaline with a slight excess of ammonia. This liberates the alkaloidal bases, which are sparingly soluble in water, and they are then finally extracted by shaking with several successive portions of chloroform. The combined chloroformic extractions are washed in another separating funnel with a small portion of water and then run into a flask. The chloroform is recovered by distillation (Fig. 5), about 2 ml. of absolute alcohol is added to the residue and then evaporated off, and the residual

alkaloid is dried at 100° C. for half an hour. This serves to remove all traces of ammonia.

The alkaloidal residue is now dissolved in an excess of fiftieth normal hydrochloric acid and the excess titrated with fiftieth normal sodium hydroxide, employing methyl red as indicator. Each ml. of fiftieth normal acid is equivalent to 0·005784 gm. of alkaloid, calculated as hyoscyamine.

Indian belladonna, *Atropa lutescens*, contains rather less hyoscyamine than the European variety but, in addition, there is present an appreciable proportion of volatile alkaloids. The latter do not possess the therapeutic activity characteristic of hyoscyamine and in the Fifth

Fig. 4.—SEPARATING FUNNELS IN USE FOR ALKALOIDAL ASSAYING

These determinations are usually conducted in duplicate and the illustration shows four funnels arranged on a stand for this purpose.

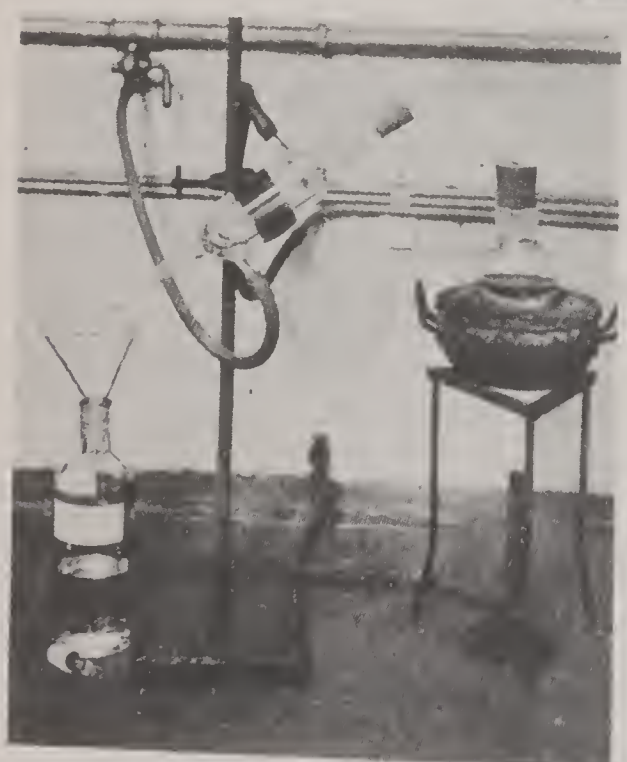


Fig. 5.—RECOVERING THE CHLOROFORM USED IN THE ASSAY OF AN ALKALOIDAL DRUG PRIOR TO THE FINAL TITRATION OF THE ALKALOID

Addendum to the British Pharmacopœia 1932 it is directed that in applying the assay to Indian belladonna the final alkaloidal residue should be dried at 100° C. for 2 hours or until moistened red litmus paper held above the heated alkaloids does not change colour.

Assay of Galenicals of Belladonna, etc.

The galenicals of the solanaceous group of drugs are also assayed by methods similar to

the foregoing, the preliminary treatment differing with the nature of the preparation.

In the case of the liquid extracts, measured volumes are transferred directly to the separating funnel and the shaking-out process is commenced at once ; tinctures are first evaporated to low bulk, and because they are much weaker than the corresponding liquid extracts, it is necessary to take much larger initial quantities for the assay. Dry extracts may be dissolved in diluted alcohol and the resulting solutions then treated by the shaking-out process.

Fig. 6.—TITRATING THE FINAL ALKALOIDAL RESIDUE WITH FIFTIETH NORMAL ALKALI AFTER IT HAS BEEN DISSOLVED IN A MEASURED EXCESS OF FIFTIETH NORMAL ACID

Vitali's Identification Test

All alkaloids of this group, excepting artificial derivatives like homatropine, produce a violet colour when tested by Vitali's reaction. This is conducted by mixing a drop of nitric acid with a trace of the alkaloid, evaporating to dryness and moistening the residue with an alcoholic solution of potassium hydroxide.

Uses of Belladonna

Belladonna is used by physicians for a variety of purposes. Its action is essentially sedative and it is a useful drug when treating colic, spasmodic asthma and whooping cough. External applications of belladonna are employed to allay inflammation, while its property of arresting sweat secretion is useful in checking excessive perspiration such as occurs in phthisis. The alkaloids of belladonna, particularly atropine, are extensively used in ophthalmic work for dilating the pupils.

Preparations from the Leaf

These include " powdered belladonna," which is the powdered leaf, assayed and adjusted to contain 0·3 per cent. of total alkaloids, a tincture and a dry extract. The tincture is made by the standard percolation process, using 70 per cent. alcohol, and is standardised on its alkaloidal

content. Dry extract of belladonna is extensively used for making pills and is prepared by percolating the powdered leaf with 70 per cent. alcohol, assaying the percolate for alkaloids and for total solids, and adding sufficient finely powdered and standardised belladonna leaf to produce, on drying, an extract containing 1 per cent. of alkaloids.

The green extract of belladonna is a preparation which is frequently used. This is made by pressing out the juice from the fresh leaves and young branches of the plant, heating the expressed liquid to about 50° C. and straining through calico to remove the bulk of the chlorophyll. The strained liquid is now heated to 93° C. and the coagulated albumin filtered off; the filtrate is evaporated to the consistency of a thin syrup and mixed with the separated chlorophyll and the preparation finally heated gently until a soft extract is obtained. The finished product should contain about 1 per cent. of total alkaloids.

Fig. 7.—Hyoscyamus

These leaves are from the annual variety and are approximately 16 cm. long. The very prominent midrib should be noted.

Preparations from the Root

Galenicals made from the root include a liquid extract, a liniment and belladonna plaster. In making the liniment a liquid extract is first prepared by the standard percolation process and the preparation finished by adding camphor and sufficient diluted alcohol to give a product containing 0·375 per cent. of total alkaloids. In order to make belladonna plaster a soft extract is prepared by the usual method, standardised for its alkaloidal content, and then mixed with the appropriate quantity of previously melted plaster of colophony. Plaster of colophony consists of a mixture of colophony and lead plaster which, in its turn, is made by treating a mixture of lead monoxide and olive oil with boiling water until the two former ingredients have combined to form a lead soap, which is then washed to remove glycerin and finally freed from excess water.

HYOSCYAMUS

Hyoscyamus niger, or henbane, is a common herb distributed over Europe and extending eastwards to India. There are two varieties, an

annual and a biennial, both of which are cultivated for medicinal purposes in England and on the Continent. The commercial drug consists of the dried leaves and flowering tops. The leaves vary considerably in size, the largest being about 25 cm. long with an elongated triangular shape. They bear numerous glandular hairs on both surfaces and possess a broad midrib, while the margins are dentate or pinnatifid. The flowers have a yellowish corolla veined with purple lines and tend to be grouped closely together.

Chemistry of Hyoscyamus

This drug contains a much smaller proportion of total alkaloids than belladonna, the average amount in the dried drug being about 0·08 per cent. consisting mostly of hyoscyamine. The proportion of hyoscine in the total alkaloids of hyoscyamus is greater than it is in the alkaloids of belladonna.

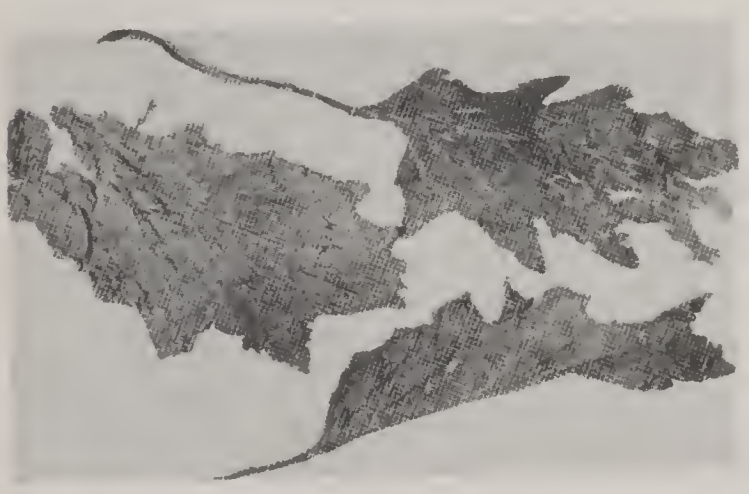


Fig. 8.—Hyoscyamus

These dried leaves are derived from the biennial henbane. The leaves, apart from the stalks, are about 25 cm. in length.

Assay of Hyoscyamus

The evaluation of this drug is conducted by the same general method as already described for belladonna. As, however, the proportion of alkaloids is so much less, a greater quantity of the drug must be taken for the operation which, in turn, necessitates slight modifications in the subsequent procedure.

Uses and Pharmacy of Hyoscyamus

Hyoscyamus is used for its sedative properties in the treatment of insomnia and also to prevent the griping caused by purgative medicines.

The galenical preparations of this drug are similar to those of belladonna, and do not call for individual description. It should, however, be stated that hyoscyamus is not usually employed in the form of liniment or plaster. In Table IV the alkaloidal strength of all the more important preparations of the solanaceous drugs is indicated.

TABLE IV—ALKALOIDAL STRENGTH OF SOLANACEOUS DRUGS AND SOME OF THEIR PREPARATIONS

Preparation	*Alkaloid per cent.*	*Remarks*
*Belladonna root	0·4 to 0·8	Exceptionally, may contain 1 per cent. alkaloid.
*Belladonna leaf	0·4 to 0·8	The alkaloid is mostly hyoscyamine.
*Powdered belladonna leaf B.P.	0·30	Standardised by assay.
*Dry extract of belladonna ..	1·0	—
*Liquid extract of belladonna ..	0·75	—
Belladonna ointment	0·6	This is made by mixing evaporated liquid extract with lard and wool fat. It is no longer an official preparation.
*Liniment of belladonna ..	0·375	—
*Plaster of belladonna	0·25	The Pharmacopœia specifies this as an approximate standard.
*Tincture of belladonna ..	0·03	—
*Belladonna suppository ..	1/60 grain in each	—
*Atropine eye ointment ..	0·25 (atropine sulphate)	—
*Atropine and mercuric oxide eye ointment	0·125 (atropine sulphate)	—
*Lamella of atropine	1/5000 grain atropine sulphate in each	—
*Hyoscyamus leaves and flowering tops	0·04 to 0·14	The total alkaloids contain a larger proportion of hyoscine than those of belladonna.
*Dry extract of hyoscyamus ..	0·3	—
*Liquid extract of hyoscyamus	0·05	—
*Tincture of hyoscyamus ..	0·005	—
*Stramonium leaves and flowering tops	0·1 to 0·3	Consists of hyoscyamine associated with hyoscine.
*Tincture of stramonium ..	0·025	—
Egyptian hyoscyamus ..	0·5 to 1·0	Commercial source for atropine.
Datura metel	0·25 to 0·55	Commercial source for hyoscine.

* Included in the British Pharmacopœia 1932.

STRAMONIUM

The thornapple, *Datura Stramonium*, grows wild in parts of southern Europe and is cultivated in England, Germany and France. The greyish-green ovate leaves vary from 8 to 25 cm. in length. The margin is formed into pointed teeth with an acuminate apex, while the under surface reveals well-marked veins leaving the midrib at an angle of about 45° and dividing towards the edge of the leaf. The white or purple flowers are solitary. The drug possesses a slight disagreeable and characteristic odour.

Chemistry of Stramonium

Dried stramonium leaves contain from 0·1 to 0·3 per cent. of total alkaloids consisting of hyoscyamine and hyoscine. The drug is assayed by the method used for the evaluation of belladonna.

Uses and Pharmacy of Stramonium

This drug is mainly used to relieve spasmodic asthma. Also it has lately been employed with some success in relatively large doses for the treatment of post-encephalitic Parkinsonism. This is a condition resembling paralysis agitans which very frequently follows sleepy sickness. The tincture, made with 45 per cent. alcohol by the percolation method, is frequently administered in association with tincture of lobelia and potassium bromide. A compound powder contains 50 per cent. of stramonium and 6 per cent. of lobelia together with anise fruit, tea leaves, oil of eucalyptus and 25 per cent. of potassium nitrate. The preparation is used as a palliative for asthma by pressing half a teaspoonful into a cone, lighting the top and inhaling the resulting fumes.

HYOSCYAMINE AND ATROPINE

The isolated alkaloids, characteristic of the solanaceous drugs, are important medicaments, particularly for ophthalmic work. They are not usually extracted from any of the foregoing drugs but from the stems of a species of henbane known as *Hyoscyamus muticus*, which is indigenous to Egypt, the Sudan and India, and may contain nearly 1 per cent. of total alkaloids.

Isolation of Hyoscyamine

The powdered Egyptian henbane is extracted by percolation with hot alcohol, the solvent removed by distillation under reduced pressure and the remaining extract poured into a 1 per cent. aqueous solution of hydrochloric acid. The acid liquid is filtered from separated resinous matter and further purified by shaking with petrol. After the latter

has been separated the acid liquor is neutralised with dilute ammonia and set aside to allow further resinous material to settle out. The clear liquid is then poured off, rendered alkaline with ammonia and the precipitated alkaloidal material extracted with chloroform. In order to remove the last traces of plant extractive the alkaloids are extracted from the chloroformic solution by shaking with dilute acid, the separated acid layer is filtered, rendered alkaline with ammonia and again extracted with chloroform. After distillation of the chloroform, the alkaloid is converted by neutralisation with oxalic acid into the oxalate. On recrystallising this salt from water lævo-hyoscyamine oxalate is obtained. Pure hyoscyamine can be isolated from this salt by dissolving it in warm water, liberating the alkaloid with ammonia and extracting with chloroform.

Preparation of Atropine

As already stated, atropine is the optically inactive form of hyoscyamine, which means that it is a mixture in equal proportions of dextro- and lævo-hyoscyamine. To prepare atropine the optically active crude alkaloids are racemised by dissolving in a 0·8 per cent. alcoholic solution of sodium hydroxide and allowing to stand until the mixture shows no optical activity when examined in a polarimeter. It is then neutralised with oxalic acid, the alcohol removed and the salt purified by recrystallisation from water. The atropine base is regenerated as in the case of lævo-hyoscyamine. The sulphate, which is the salt usually employed in pharmacy, can be obtained by adding a 10 per cent. solution of sulphuric acid in absolute alcohol to a dry ethereal solution of the base, when atropine sulphate separates as a white micro-crystalline powder.

Uses and Pharmacy of the Alkaloids

The sulphates of both atropine and hyoscyamine are used for making solutions for hypodermic injection, the former for the relief of pain in sciatica and as an antispasmodic in asthma, the latter for severe nervous excitement. Both alkaloids are very toxic but hyoscyamine is the more potent. Lamellæ (eye discs) of atropine, consisting of very small gelatin discs containing 1/5000th of a grain of atropine sulphate, are used for ophthalmic work. In addition, special eye ointments containing atropine sulphate alone or mixed with yellow mercuric oxide are also extensively employed.

Homatropine

An artificial alkaloid belonging to this group and called homatropine is also widely used for its mydriatic property. It is prepared by heating together tropine, obtained by hydrolysing crude atropine, and mandelic

acid in a stream of hydrogen chloride gas. It is considerably less toxic than atropine.

HYOSCINE OR SCOPOLAMINE

This important alkaloid of the solanaceous group is, like hyoscyamine, an ester of tropic acid, the base to which the acid is attached being isomeric with scopoline, $C_8H_{13}NO_2$. Scopoline resembles tropine both in structure and properties. The principal source of hyoscine is *Datura metel*, an annual plant belonging to the same genus as stramonium, and indigenous to India. It is isolated in the same manner as hyoscyamine, except that sodium bicarbonate is employed, instead of ammonia, for liberating the bases.

Hyoscine hydrobromide occurs as colourless, odourless, transparent crystals and its solutions are lævo-rotatory. It is a valuable hypnotic and sedative and is often used as a preliminary to general anæsthesia for surgical work. For this purpose 1/100th grain combined with 1/6th grain of morphine hydrochloride is given hypodermically about an hour and a half before an operation and again an hour later. The anæsthesia induced is often sufficient but, if necessary, a little ether may be inhaled to complete it. Under the name " twilight sleep " this form of narcosis has been used with success for childbirth.

Hyoscine has once figured in the annals of criminology. In October, 1910, Crippen was convicted of poisoning his wife by administering hyoscine hydrobromide. Dr. (later Sir William) Willcox found 25/84th of a grain of hyoscine in the body of the victim, and he was able to demonstrate that the extracted alkaloid gave a positive reaction when examined by Vitali's test.

Chapter IV

CINCHONA

CINCHONA has been known for more than three centuries as an invaluable medicine for the treatment of malaria. In former days it was called Peruvian Bark from the country of its origin. Linnæus, in his botanical classification of 1742, named the tree from which the bark is obtained "cinchona," because its general use for the treatment of malaria originated with its successful employment in curing the Countess of Chinchon, Spanish Vicereine of Peru, in the year 1638.* The difference in the spelling was the result of Linnæus being misinformed as to the correct title of the Countess.

Fig. 1.— CINCHONA BARK

For exportation the bark is pressed by hydraulic pressure into firm bales (in Ceylon) or stamped into sacks (in Java). A growth of lichen is well seen in this illustration.

The Cinchona Tree

Cinchona is a handsome evergreen tree often attaining a height of 100 ft. Several species are known, all of which

* According to A. W. Haggis (*Bulletin of the History of Medicine*, 1941, **10**, 417, and *British Medical Journal*, 1942, I, 299) this oft-repeated story is not true. A few years ago Miss I. A. Wright, searching in the *Archivio Generale de Indias* at Seville on behalf of the late Sir Henry Welleome, discovered the official diary of the Count of Chinchon, which was kept with scrupulous care by his secretary, Dr. Don Antonio Suardo. From this it appears that the Countess never suffered from malaria or any other febrile disorder during the eleven years that she remained in Peru ; but when the Count and Countess were at last on their way homeward bound for Spain the latter, on reaching Cartagena, Colombia, was struck down by a disease, which was probably yellow fever, and died there on February 28th, 1641. The Count *did* suffer from recurrent fever during his residence in Peru, but the diary does not record any remarkable cure, the treatment having always consisted in repeated bleeding, together with prayers in all the monasteries and convents in the city of Lima.

About this time it appears that the bark of a tree locally known as "quinua-quinua" or "quina-quina" and identifiable as *Myroxylon peruiferum* was exported to Spain and Italy whence "Peruvian balsam" was obtained and used in Rome and other cities as a febrifuge. When the demand for this drug exceeded the supply, exporters adulterated it with what is now known as cinchona bark, a subterfuge so well received that eventually the adulterant alone was supplied but still under the old name of "quina-quina."

are indigenous to the spurs of the Andes from Colombia through Ecuador and Peru to Bolivia. There, in a warm and moist climate, it grows at an elevation between 5000 and 7000 ft.

Transplantation of Cinchona

Owing to the wasteful way in which the drug was collected, by simply felling the trees and stripping the bark, available supplies became scarce about the middle of the nineteenth century and scientific expeditions to South America were organised with the object of transporting seedlings to India. After many difficulties and hardships, Sir Clements Markham succeeded in establishing the cultivation of the cinchona tree in the Nilgiris and the Palnai Hills of Travancore. A little later plantations were extended to Mysore, Darjiling and the Karen Hills of Burma. The species chosen by Markham for transplantation to India were *Cinchona Calisaya*, *C. officinalis* and *C. succirubra*.

In 1855 Charles Ledger transferred some seedlings of *Cinchona Calisaya* to India, and also some of the same batch to Java. Ledger's plantations in India failed, but those in Java, under the care of very skilful Dutch planters, flourished so well and produced a strain of trees so rich in active principles that the plant is now regarded as a separate variety under the name *Cinchona Ledgeriana*. Fifty years ago nearly 85 per cent. of the world's supplies of cinchona originated from South America and about 1 per cent. came from Java, but such has been the success of the Dutch plantation that to-day the figures are almost reversed. The Indian plantations are still being extensively worked.

Collection of the Bark

With the application of scientific cultivation the wasteful practice of felling the trees prior to removing the bark was abandoned. A method which has been successfully employed consists in cutting the bark from the living tree in long vertical pieces about an inch wide, leaving a space untouched between each denuded area. The tree is then bound round with moss and the bark allowed to grow over the wounded portions of the trunk. After sufficient time has elapsed for the formation of fresh bark the intermediate areas are stripped and the product is termed " mossed " bark. The tree is again covered and in due course the bark which has grown over the areas which were first stripped can, in its turn, be removed and is termed " renewed " bark.

Owing to labour costs the above method is being discontinued, and it is now more usual either to uproot the tree and thereby derive the additional profit arising from the sale of the root bark or to cut the trees down to form stools from which shoots will arise capable of yielding quills of bark. This latter product is especially favoured for druggists' use.

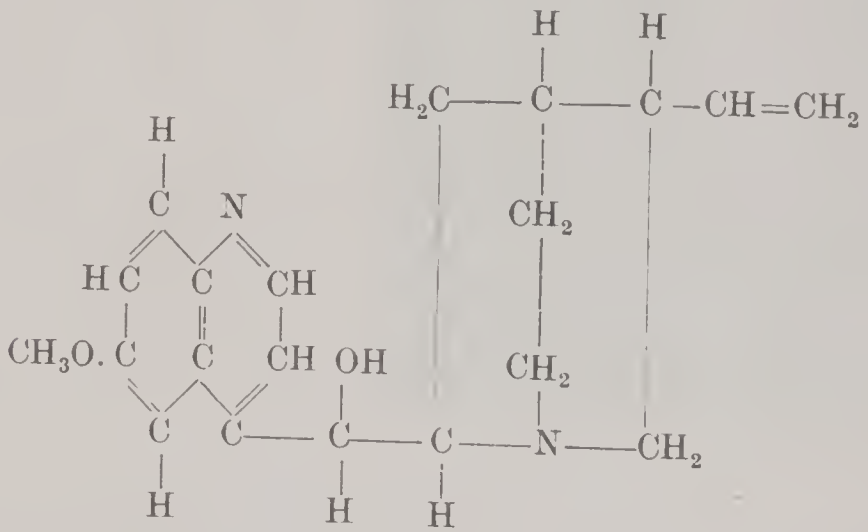
Description of the Bark

Several species of cinchona are found in commerce which exhibit differences in colour and surface details. In general, the bark from the tree stems occurs in quilled pieces of variable thickness and length. The rough outer surface is grey, or brownish-grey, showing both transverse and longitudinal fissures and often bearing lichens ; the inner surface is striated and varies in colour from yellowish-brown to deep red-brown. The bark possesses a slight odour and a bitter astringent taste. The root bark is usually met with in short curved or twisted pieces not more than 7 cm. long. It is marked externally by conchoidal depressions. Both surfaces are of the same colour but in other general characteristics it resembles the stem bark.

Chemistry of Cinchona

By far the most important constituent of cinchona is the alkaloid quinine. In addition, twenty-nine other alkaloids have been isolated, of which cinchonidine, which like quinine is lævo-rotatory, and the two dextro-rotatory alkaloids quinidine and cinchonine are of most significance. The remaining alkaloids only occur in small proportion and, as they have no special application in commerce, there would be little point in giving a list of their names. The alkaloids occur in the bark as salts of quinic acid, $C_7H_{12}O_6$, and of cinchotannic acid, $C_{14}H_{16}O_9$.

The constitution of quinine is generally considered to be represented by the following graphical formula due to Königs.



This formula will also represent the structure of its stereoisomeride quinidine while the formula for the two stereoisomeric alkaloids cinchonine and cinchonidine only differs by the replacement of the methoxy group, CH_3O, by a hydrogen atom.

The proportion of quinine, cinchonidine and other alkaloids present in the bark varies considerably with the source and species. A fair sample of Calisaya bark may contain 6 to 7 per cent. of total alkaloids of which perhaps 4 per cent. may be quinine and about 1 per cent. cinchonidine. Ledgeriana varieties of the drug often contain very much more quinine, even up to 8 or 10 per cent., while the proportion of other alkaloids is relatively small.

The colouring matter in the bark, called cinchona red, has the empirical formula $C_{12}H_{14}O_7$ and may be present to the extent of 10 per cent. It is soluble in alkalis, but is re-precipitated by acids. The only other constituents that need be mentioned are the very bitter glucosides called α-quinovin and β-quinovin.

Assay of Cinchona Bark

The evaluation of this drug aims at the determination of total alkaloids and also the proportion of quinine and cinchonidine. No particular virtue attaches to the presence of the latter substance but, as both the alkaloids form sparingly soluble tartrates, it is possible to effect a separation of these from the other bases and thereby arrive at a fair estimate of the quantity of quinine present in the bark, since the amount of cinchonidine rarely exceeds 0·8 per cent. The quantitative isolation of the alkaloids in a state of purity is a difficult problem and new methods are frequently proposed. The following method of extraction is due to P. A. W. Self and C. E. Corfield.

Fig. 2.—ASSAYING CINCHONA BARK

This picture shows the powdered drug being transferred to the extraction apparatus after it has been macerated with lead subacetate solution and ammoniacal alcohol.

Assay for Total Alkaloids

Ten gm. of the powdered drug is mixed with 20 ml. of a mixture of lead subacetate solution and water and after an hour 50 ml. of ammoniacal alcohol (containing 2·5 per cent. by volume of strong ammonia solution) is added. After standing for a further hour the mixture is transferred to a continuous extraction apparatus in the manner shown in Fig. 2, using

about 50 ml. more of the ammoniacal alcohol and then attaching the extractor to a refluxing condenser and boiling the solvent for at least 4 hours (Fig. 3).

Most of the alcohol in the flask, which now contains the alkaloids, is removed by evaporation and about 50 ml. of very dilute sulphuric acid added and the mixture boiled, allowed to cool, and then filtered through a pledget of cotton-wool into a separating funnel. The flask is washed out with several portions of dilute acid and the washings also filtered into the separating funnel. When all alkaloid has thus been transferred to the acid solution the latter is shaken with chloroform. The separated chloroformic layer is drawn off into another separating funnel, agitated with a fresh portion of dilute acid and, after separation, is rejected.

The acid liquid in the first separating funnel is shaken twice more with chloroform, each chloroformic layer being shaken with the dilute acid in the second separating funnel before rejection. This process removes the last traces of non-alkaloidal extractive matter from the acid, while the treatment with acid in the second separating funnel prevents any possible escape of alkaloid by way of the chloroformic washings.

The acid liquid in the second separating funnel is now added to that in the first and the combined acid liquids are rendered alkaline with dilute ammonia solution.

The liberated alkaloidal bases are now completely extracted by shaking with successive portions of chloroform, each chloroformic extract being washed in turn in another separating funnel with a little water, the same water being used for each successive extract. The combined chloroformic extracts are transferred to a tared flask, the chloroform removed by distillation, a little alcohol added and at once evaporated off, and the total alkaloids weighed after drying at 100° C.

Assay for Quinine and Cinchonidine

The total alkaloids from the above determination are dissolved in a mixture of normal sulphuric acid and 50 per cent. alcohol, the solution boiled and then neutralised with decinormal sodium hydroxide using hæmatoxylin as indicator. The mixture should be boiled during the process of neutralisation, then cooled, and rendered just acid by the addition of a few drops of decinormal sulphuric acid. The mixture is again boiled and, if necessary, a few more drops of the same acid added so that the colour of the indicator is just yellow.

The hot solution is now filtered into another flask and all the alkaloid completely transferred by repeatedly washing the first container with small portions of boiling water and passing the washings through the filter. The filtrate is evaporated to a convenient bulk and then about a fourth its weight of powdered sodium potassium tartrate added and, after the salt has dissolved, the mixture is set aside for 24 hours. The precipitate of quinine and cinchonidine tartrates is filtered off on a

hardened filter paper and washed with a 25 per cent. solution of sodium potassium tartrate.

The filter paper with the precipitate is now macerated for some time with 20 per cent. sodium hydroxide solution in order to decompose the alkaloidal salts, the mixture then transferred to a separating funnel and the quinine and cinchonidine completely extracted with chloroform in the usual way, the chloroformic extracts being washed with a little water and transferred to a tared flask. The chloroform is removed by distillation, a little alcohol added and at once evaporated off, and the quinine and cinchonidine weighed after drying at 100° C.

Cinchona bark is officially required to contain not less than 6 per cent. of total alkaloids of which not less than half must consist of quinine and cinchonidine.

Fig. 3. — EXTRACTION APPARATUS USED IN THE ASSAY OF CINCHONA

This consists of a straight glass tube, supported by a wire frame, within a wider tube attached to a flask below and a condenser above. The lower end of the inner tube is flanged and covered with a piece of calico. A pledget of cotton wool holds the powdered drug in place.

Pharmacy of Cinchona

Galenical preparations of cinchona are employed as bitter tonics while certain of them are useful as astringent gargles.

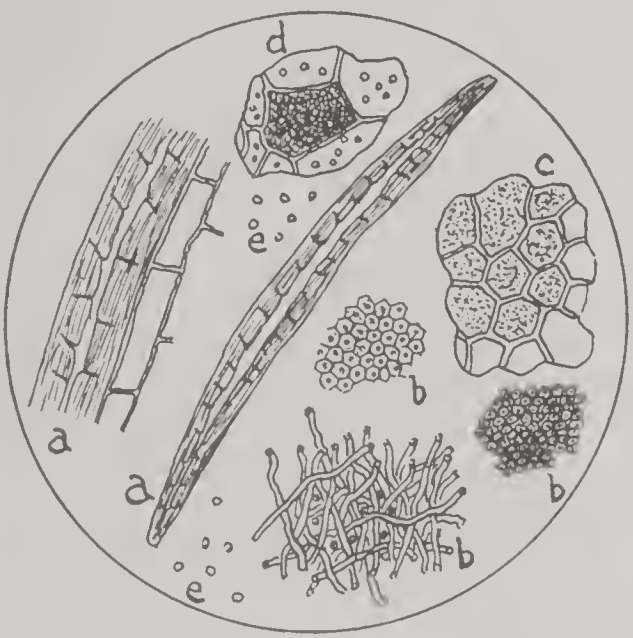


Fig. 4.—DIAGRAMMATIC REPRESENTATION OF THE TYPICAL HISTOLOGICAL ELEMENTS OF POWDERED CINCHONA BARK AS SEEN UNDER THE MICROSCOPE (× 180)

a, bast fibres; b, debris of lichens; c, cork; d, cells containing sandy crystals of calcium oxalate, surrounded by cortical parenchyma; e, starch grains.

Extract of cinchona, which is principally used for making other galenicals, is standardised to contain 10 per cent. of total alkaloids, and is prepared by percolat-

ing the powdered bark to exhaustion with alcohol, removing the solvent by evaporation and dissolving the residue in glycerin. Tincture of cinchona contains 1 per cent. of total alkaloids and is made by suitably diluting the extract with 70 per cent. alcohol. The compound tincture consists essentially of a solution of the extract in 70 per cent. alcohol which contains the extractive matter from approximately 5 per cent. each of dried bitter-orange peel and serpentary rhizome. The preparation is coloured with cochineal and contains 0·5 per cent. of the total alkaloids of cinchona. Decoction of cinchona, made by boiling 6·25 parts of the powdered bark with water for 10 minutes, cooling, straining and diluting to 100 parts, is sometimes added to astringent gargles.

The preparations of cinchona are assayed by methods similar to that adopted for the bark, omitting, of course, the preliminary extraction with ammoniacal alcohol.

QUININE

The greater part of the world's production of cinchona is employed for the manufacture of quinine which is used in enormous quantities as a specific against malaria.

Isolation of Quinine

The dried and powdered bark is treated with 30 per cent. of its weight of sifted slaked lime and 90 per cent. of a 5 per cent. aqueous solution of caustic soda. The mixture is extracted in a steam-heated rotating ball mill with hot heavy petroleum which dissolves the alkaloids. After some hours of constant agitation the mixture is allowed to settle and the petroleum drawn off. Further extractions are made and the mixed petroleum liquors shaken with sufficient hot diluted sulphuric acid to form the neutral sulphates of the alkaloids. The oil is separated while hot and the neutral aqueous liquid cooled, when quinine sulphate separates out and is subsequently purified by recrystallisation from water, animal charcoal being used to decolorise the product. Quinine alkaloid itself may be obtained from the sulphate by dissolving the latter in a large volume of water containing a little sulphuric acid and pouring the liquor into dilute aqueous sodium carbonate solution ; the precipitated quinine is filtered off and washed. The alkaloid is then carefully dried, first in a centrifugal machine, and subsequently in a dark drying room at a temperature not exceeding 30° C.

Properties of Quinine

Quinine is a white granular powder very sparingly soluble in water, more soluble in dilute ammonia and readily dissolved by acid solutions. When the latter are treated with Mayer's reagent a copious white preci-

pitate is produced (Fig. 5), a reaction which is given by the majority of alkaloids. Solutions of quinine in dilute sulphuric acid exhibit a blue fluorescence. The same phenomenon is manifested when the alkaloid is dissolved in acetic or aqueous tartaric acid solution but does not occur with other common acids.

Fig. 5.—MAYER'S TEST

The right-hand watch glass contains a trace of quinine dissolved in dilute sulphuric acid and has yielded a white precipitate with Mayer's reagent. The test on the left in which quinine was absent remained quite clear. This reaction is given by the majority of alkaloids, but there are a few exceptions.

The Thalleioquin Reaction

If a few drops of bromine solution are added to about 5 ml. of a 0·1 per cent. solution of quinine in dilute sulphuric acid and the mixture rendered just alkaline with ammonia an emerald-green colour is produced. This test, known as the thalleioquin reaction, is given by quinine and quinidine, but not by cinchonine or cinchonidine.

Salts of Quinine

The neutral salts of the common acids are only sparingly soluble in water but the acid salts dissolve readily. Quinine sulphate $(C_{20}H_{24}O_2N_2)_2.H_2SO_4.7\frac{1}{2}H_2O$ dissolves in 800 parts of cold water while the bisulphate $C_{20}H_{24}O_2N_2.H_2SO_4.7H_2O$ is dissolved by 10 parts of water. The neutral and acid hydrochlorides are also used in considerable quantity.

Kerner's Test for Other Alkaloids

It is important that salts of quinine used for medicinal purposes should not contain an undue proportion of the other cinchona alkaloids. Kerner's test, which depends upon the fact that quinine is more soluble in dilute ammonia than the other cinchona alkaloids, imposes a limit for these impurities. The test is applied to quinine sulphate in the following manner : 1 gm. of the sample is added to 30 ml. of water contained in a flask which is then attached to a reflux condenser. The mixture is boiled until the quinine sulphate has mostly dissolved, then quickly cooled to 15° C. and maintained at that temperature for half an hour. The liquid is rapidly filtered off and 5 ml. of the filtrate transferred to a test tube or measuring cylinder. A 10 per cent. solution of ammonia is

now run in from a burette until, on agitating the mixture, the white precipitate first formed redissolves, yielding a clear solution.

Good samples of quinine sulphate usually require 5 ml. of ammonia to produce a clear mixture. If more than 6·5 ml. is required the sample should be viewed with suspicion. Fig. 6 shows the completion of two tests in which one has passed but the other failed. It is important that the ammonia should be added very quickly, and it is customary to repeat the final operation on another portion of the filtrate when it has been approximately ascertained how much ammonia will be required. In order to examine salts other than the sulphate it is first necessary to extract the quinine from them and convert it into the neutral sulphate, since the conditions of the test are empirical and unsuited for direct application to other compounds of quinine.

Fig. 6.—KERNER'S TEST FOR THE PRESENCE OF OTHER CINCHONA ALKALOIDS IN QUININE SULPHATE

This shows the completed test. The left-hand tube indicates quinine sulphate of good quality, but the test on the right has revealed a sample containing an unduly high proportion of cinchona alkaloids other than quinine.

Ammoniated Tincture of Quinine

This well-known preparation, so frequently used for the treatment of the common cold, consists of a 2 per cent. solution of quinine sulphate in approximately 50 per cent. alcohol containing about 3 per cent. of ammonia. The merit of quinine as a prophylactic against colds is probably connected with its antipyretic properties. For the treatment of malaria, tablets of the various salts are very extensively employed, while, for the sake of economy, preparations of the mixed alkaloids of cinchona find a wide application in India. The latter is officially recognised in the British Pharmacopœia 1932 under the name Totaquine which is required to contain not less than 70 per cent. of crystallisable cinchona alkaloids, of which not less than one-fifth is quinine.

In association with the scientific control of the mosquito, this drug

has furnished immeasurable assistance to the white races in their commercial conquest of the tropical regions of the world.

ALSTONIA

Alstonia is sometimes used in India and the Eastern Colonies and in Australasia as a bitter tonic and as a remedial measure for the treatment of malaria, but for the latter purpose it cannot compare with cinchona. The drug used in India consists of the dried bark of *Alstonia scholaris* while the bark of *A. constricta* is limited to Australasia. It is said that the specific name *scholaris* refers to the fact that slabs made from the wood of this handsome tree were used as school-slates, the letters being traced upon them in sand. The active principles are alkaloidal in character and the drug is usually employed in the form of an infusion or as a 1 in 8 tincture made with 60 per cent. alcohol.

Chapter V

ERGOT

ERGOT, the only vegetable drug in general use referable to the fungi, has in recent years been the subject of considerable scientific research which has led to the production of better galenicals, more accurate standardisation and improved clinical technique. It is a drug of great importance, owing to its value in the treatment of hæmorrhage following childbirth.

Description

Ergot is the sclerotium, or resting stage, of a parasitic fungus *Claviceps purpurea*, which infects the flower of the rye plant and occasionally other cereals and grasses. Fig. 1 shows an ear of rye with the "grains" or "corns," which are violet or nearly black curved rods, varying from 15 to 35 mm. in length and 3 to 7 mm. in diameter. The curved grains taper towards both ends and, besides being longitudinally furrowed on the concave side, often bear numerous transverse fissures. Ergot breaks with a short fracture exhibiting a white or pinkish interior. It has a characteristic taste and disagreeable odour.

Fig. 1. — ERGOT GROWING ON AN EAR OF RYE

Life Cycle of the Fungus

Under natural conditions the ergot grain falls to the ground in the autumn and germinates in the spring by developing stalks having terminal knobs, called spheridia, mottled by minute warts (Fig. 3). Each wart covers a cavity containing the primitive sexual elements which in late summer generate vast numbers of ascospores. These latter are carried by air currents and, after settling on the rye flowers, germinate, forming masses of threads termed the sphacelia. These in turn produce asexual spores and, at the same time, induce the rye flower to secrete honeydew, which, with the spores, is carried by insects to other rye plants where full sphacelia then develop directly from the asexual

Fig. 3.—A "GRAIN" OF ERGOT GERMINATING
A frosty winter favours vigorous growth in the following spring.

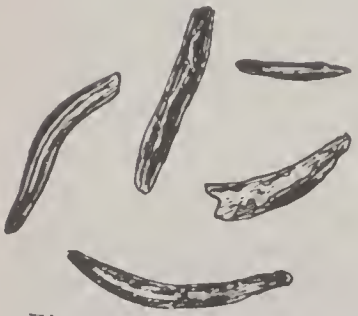


Fig. 2. — "GRAINS" OR "CORNS" OF ERGOT AS SEEN IN COMMERCE

An old German name for ergot is Mutterkorn ("Mother corn"), which suggests a long-standing acquaintance with its medicinal action.

spores. The sphacelia, from either source, rapidly grow and consolidate themselves, forming the relatively hard sclerotia, or ergot grains, which tide the fungus through the winter in readiness to repeat the cycle of its life.

Sources of Ergot

The principal areas of production are Poland and Russia, and the north-western corner of the Iberian peninsula, including parts of both Portugal and Spain. The collection of ergot is a peasant industry, and supplies vary according to the prevailing climatic conditions; wet weather, as would be expected of a fungus, favouring a plentiful supply. Attempts at artificial cultivation in other countries have, so far, failed as commercial propositions, owing to the high labour costs involved. The consumption of ergot in Great Britain has been estimated at about 20 tons per annum.

Alkaloidal Constituents of Ergot

Several alkaloids have been identified in ergot of which the most important is the water-soluble base ergometrine ($C_{19}H_{23}O_2N_3$), discovered in 1935 by H. W. Dudley and J. Chassar Moir in this country and by a team of investigators working in the United States whose results were published a few weeks later. Prior to the discovery of ergometrine the alkaloid ergotoxine ($C_{35}H_{39}O_5N_5$), originally isolated and characterised by G. Barger and F. H. Carr in 1906, was regarded as the most important physiologically active principle. Ergotoxine, which is a water-insoluble alkaloid, occurs to the extent of about 0·18 per cent. in good specimens of Spanish or Portuguese ergot, but Russian and Polish material rarely contains more than 0·01 per cent. The amount of ergometrine present in ergot is much less, being only about 0·01 per cent. in the drug derived from southern Europe while the other varieties which are low in ergotoxine content are correspondingly poor sources of ergometrine. Ergotoxine in the form of one of its soluble salts, usually the ethanesulphonate, will induce a satisfactory physiological response provided it is administered by intramuscular injection, whereas ergometrine will promote contraction of the human uterus within a few minutes even when given orally; moreover, the latter alkaloid is less toxic than ergotoxine. Associated with these are two physiologically inactive alkaloids, namely, ergotinine which is insoluble in water, and ergometrinine which is isomeric with ergometrine and is water-soluble. Ergotinine was the first crystalline alkaloid of ergot to be isolated and was discovered in 1875 by C. Tanret; it is isomeric with ergotoxine and can be converted into the phosphate

for the latter alkaloid by treating it with boiling absolute ethyl alcohol containing a little phosphoric acid. Ergotinine has now been resolved into two isomeric bases having optical rotatory power of opposite sign : the complement alkaloid is termed pseudo-ergotinine. In ergot of Festuca grass another alkaloid, called ergotamine, is predominant ; it is similar to, but not chemically identical with, ergotoxine and associated with it is a physiologically inactive counterpart termed ergotaminine.

Non-alkaloidal Constituents

Two amine bases occur in ergot, namely, tyramine (*p*-hydroxyphenylethylamine), $HO.C_6H_4.CH_2CH_2NH_2$, and histamine (β-iminazolylethylamine), $C_3H_3N_2.CH_2CH_2NH_2$. These bodies, and particularly histamine, are physiologically active, although less potent than ergotoxine. In fresh, well-dried ergot, the quantity of histamine is only about 0·005 per cent., but if the drug is stored under damp conditions more histamine is produced, and in old, badly preserved material 0·1 per cent. of histamine has been found ; at the same time the proportion of alkaloids rapidly falls if the drug is not kept dry.

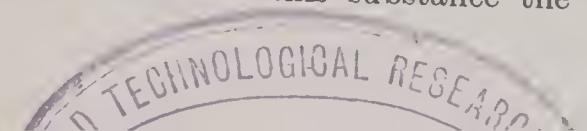
In addition to these, ergot contains three pigments, believed to be characteristic of the drug, and also about 30 per cent of fatty oil.

Isolation of Ergometrine

In the method originally adopted by Dudley and Moir 10 kg. of powdered and defatted ergot was extracted with hot dilute sulphuric acid, the acid extract filtered and treated with a slight excess of barium hydroxide solution. The precipitate of barium sulphate was filtered off and the excess of barium hydroxide removed by treatment with carbon dioxide and filtration. The clear alkaline solution was concentrated *in vacuo* and the residue treated with alcohol which precipitated non-alkaloidal extractive matter ; after concentrating the filtered alcoholic solution the residue was extracted with chloroform, and the chloroformic solution of the bases shaken with dilute sulphuric acid. After rendering the acid solution alkaline with ammonia the bases were again transferred to chloroform and the solvent evaporated to dryness, leaving a resinous residue containing crystals of ergometrine. The resinous material was carefully dissolved away by the cautious addition of chloroform, leaving the pure ergometrine which is only slightly soluble in that solvent. In one of the original experiments 0·82 gm. of water-soluble alkaloid was obtained from 10 kg. of the defatted drug.

Uses of Ergot

Ergot is principally employed for its power of promoting contraction of the uterus, and it may consequently be regarded as an oxytocic drug. This physiological property is shared by extract of the posterior lobe of the pituitary gland, but with this substance the action is transitory,



although rapid in onset. Ergot is absorbed relatively slowly, but once its action has begun the contraction is maintained for many hours. When the placenta separates from the uterus, it leaves the connecting vessels open, bleeding being stopped in the first instance by contraction of the uterine muscle, which occludes the vessels by pressure. Natural contraction often fails, and it is therefore a frequent practice with obstetricians to inject pituitary extract and administer ergot orally at the same time, whence the former drug contracts the uterus at once and arrests the hæmorrhage, while the ergot maintains the condition after the effect of the pituitary has passed away.

Pharmacy of Ergot

The British Pharmacopœia 1932 includes two preparations, a liquid extract and a standardised defatted ergot powder. Since these were formulated before the discovery of ergometrine they are both standardised with respect to their content of total alkaloid calculated as ergotoxine, but they contain the proportion of ergometrine natural to the original drug.

The liquid extract is made by macerating and percolating the powdered and defatted drug with a 1 per cent. solution of tartaric acid in 50 per cent. alcohol. The percolate is collected in portions which are assayed for their content of alkaloid and then mixed together, so that an extract containing 0·06 per cent. of total alkaloids, calculated as ergotoxine, is produced. The preliminary defatting of the powdered drug is conducted by percolation with light petroleum. The alkaloidal content of liquid extract of ergot falls on keeping even after the lapse of a few months, a fact officially recognised in the Pharmacopœia, which stipulates that the preparation shall contain not less than 0·04 per cent. of the total alkaloids after storage.

The standardised ergot powder is called prepared ergot and consists of the powdered drug deprived of its fat by percolation with light petroleum and adjusted to contain 0·1 per cent. of total alkaloids calculated as ergotoxine. The strength is regulated by mixing a sufficient quantity either of powdered defatted ergot, which contains a larger or smaller proportion of total alkaloids, or of the powder obtained by drying the marc remaining when the liquid extract has been prepared. It is convenient for oral administration for which purpose it is enclosed in gelatin capsules.

Standardisation of Ergot

The assay of this drug may be conducted by chemical or biological methods. The chemical procedures are based upon a preliminary isolation of the total alkaloids, their separation into water-soluble and water-insoluble groups and their final determination by means of a quantitative colour test. Inasmuch as the colour reaction responds to

the physiologically inert alkaloids ergotinine and ergometrinine the results of chemical assay cannot be regarded as a final criterion of potency ; on the other hand, the biological methods, while not influenced by the inert alkaloids, lack the precision of measurement characteristic of chemical assays. The biological assay described here is undoubtedly the best so far evolved, since it is based upon the action of the alkaloids on uterine muscle. It was originally devised in 1923 by W. A. Broom and A. J. Clark, when ergotoxine was regarded as the only active principle of importance present in ergot ; consequently a stable and soluble salt of ergotoxine, usually the ethanesulphonate, was employed as the standard of measurement.*

Biological Assay of Ergot

The method depends upon the property possessed by ergotoxine and ergometrine of inhibiting the motor action of adrenaline on the plain muscle of the excised uterus of the rabbit. An apparatus similar to that shown diagrammatically in Fig. 4 is employed. The ends of two strips of muscle, about 1 cm. long by 0·5 cm. wide, taken from the horn of a freshly killed rabbit's uterus, are fixed to the platinum points fused into each of the tubes D and D^1 which dip into the vessels A and A^1, the other ends being attached to threads connected to the levers B and B^1.

About 100 ml. of warm Ringer's solution is introduced into each of the baths A and A^1, the temperature of which is maintained at 37° to 40 ° C. by means of the outer water-bath heated thermostatically with an electric lamp enclosed in the sleeve C.

Ringer's solution contains 9·0 gm. of sodium chloride, 0·42 gm. of potassium chloride, 0·24 gm. of calcium chloride, 0·5 gm. of sodium bicarbonate, and 0·5 gm. of dextrose in 1 litre of water which has been distilled in glass apparatus.

A slow stream of oxygen is passed through the tubes D and D^1 and the drum of smoked paper F, driven by an electric motor, is set in motion so that it moves at the rate of 0·5 cm. per minute. Small weights are arranged on the levers B and B^1 so that the muscles are very gently distended and the whole system is steady. Adrenaline hydrochloride solution equivalent to 0·02 mgm. of adrenaline is added to each bath.

Tonic contraction of both muscles, most probably of different magnitude, should occur and last for a few minutes. If this does not happen, more adrenaline must be used, but always the same quantity should be added to each bath. The Ringer's solution is emptied out by turning taps G, G^1, and H, and a fresh supply run in by turning tap I, which is connected with a convenient reservoir provided with an arrangement for warming the liquid to 37° to 40° C. The weights on B and B^1 are so

* Recent investigations suggest that the presence of ergotoxine diminishes the action of ergometrine in the Broom and Clark method and that as the latter alkaloid, if first separated from the ergotoxine group, can itself contract the isolated rabbit's uterus when added to the Ringer's solution, it is better assayed by directly measuring this effect. Owing to the preponderating influence of ergotoxine this procedure is inapplicable to ergot or its preparations.

adjusted that on repeating the addition of adrenaline, equal contractions are recorded on the drum.

When, it may be after several trials, this object has been attained and the equal contractions have subsided, a known quantity of ergotoxine ethanesulphonate solution (say 0·5 ml. of a 1 in 30,000 solution) is added to one bath and 30 seconds later a measured quantity of a known dilution of the sample under test is added to the other bath. After 10 minutes an equal dose of adrenaline is added to each bath in turn.

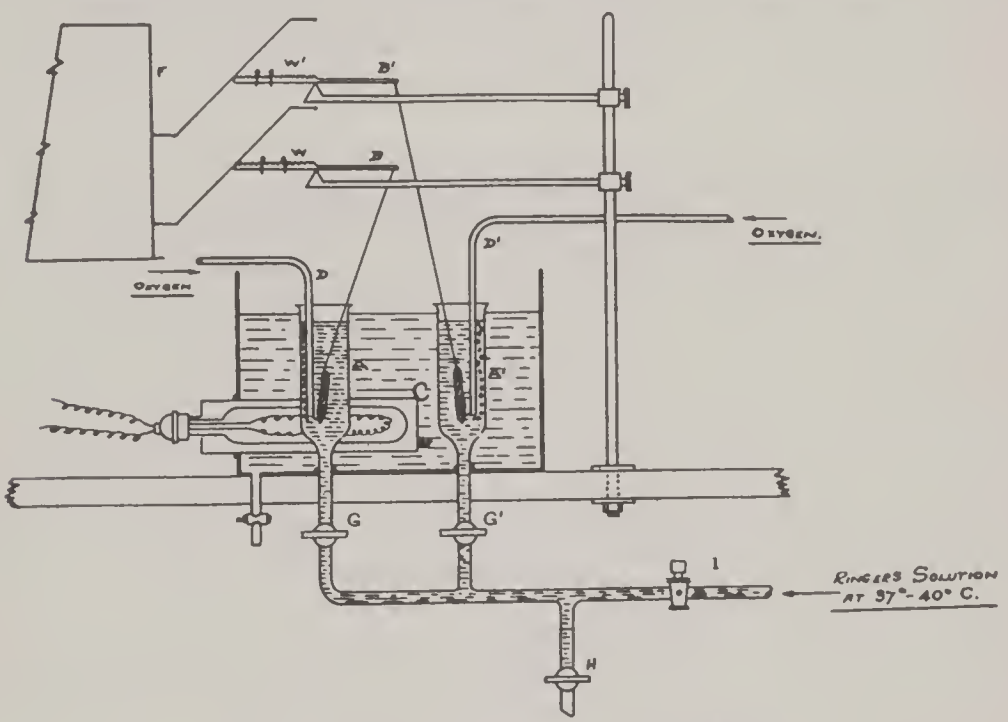


Fig. 4.—THE BIOLOGICAL ASSAY OF ERGOT

On adding equal doses of adrenaline to the baths A and A1 the muscles contract and operate the levers B and B1 which trace a line on the moving drum of smoked paper F. The movements of the levers, corresponding to the contractions, are rendered equal in magnitude by adjusting the weights W and W1. Preparations of ergot are assayed by adding a measured quantity to one of the baths so that it inhibits the contraction due to adrenaline in the same degree as a known amount of pure ergotoxine ethanesulphonate added to the other bath.

If the contraction produced by the muscle to which the standard was added is the greater, then it may be concluded that the sample contained the larger quantity of ergotoxine, because it reduced the contraction more.

If no contraction is registered by either muscle, then too much ergotoxine has been added to both.

In either case the test must be repeated, after changing the Ringer's solution, and the quantity of ergotoxine suitably altered until the contractions produced 10 minutes later by the same dose of adrenaline are

both equally diminished in magnitude. The time interval during which the ergotoxine is allowed to act is quite arbitrary and may be varied to suit the experiment. Equal diminution of contraction implies equal concentrations of ergotoxine in each bath, whence the strength of the unknown sample is readily calculated.

Like all modern biological assays, the above procedure presupposes the existence of a standard which, in this case, is a highly purified salt of ergotoxine. It may be observed here that it has been found impracticable to make biological phenomena themselves the subject of measurement ; all these assays must be comparative with reference to a standard, either absolute or adopted by international agreement.

Chemical Assay of Ergot

The present official method of standardisation is based upon a colorimetric chemical assay which was developed before ergometrine was discovered and it is essentially a measure of the total alkaloids calculated as ergotoxine since ergometrine and ergometrinine also respond to the colour reaction. As the Pharmacopœial assay is out of date, a procedure will be described, due to C. H. Hampshire and G. R. Page, whereby the water-soluble and water-insoluble group of alkaloids are separately determined. The colour reaction, which is now always used for the chemical determination of ergot alkaloids, was proposed as a qualitative test by the Dutch chemist H. W. van Urk, who found that when the alkaloids were treated under certain conditions with *p*-dimethylaminobenzaldehyde a blue-violet colour is produced. The technique of this test was greatly improved and rendered quantitative by an American investigator, M. I. Smith, and it has been still further perfected by a group of chemists in this country. The results of chemical assay generally run parallel with those obtained by the biological method, because although the test responds to all the alkaloids of ergot it usually happens that in most samples of the medicinal drug the latter contain about the same proportion of physiologically active bases, although this certainly does not hold in the case of ergots derived from grasses other than rye.

Method of Hampshire and Page for Ergot

The drug is reduced to a moderately fine powder and 10 gm. extracted, with light petroleum in a continuous extraction apparatus (see Fig. 4, page 124) until the fat is completely removed. The extracted drug is dried at a temperature not exceeding 40° C., transferred to a porcelain dish, moistened with 8 ml. of dilute solution of ammonia and mixed with sufficient anæsthetic ether to form a semi-liquid mass. Most of the ether is allowed to evaporate, the residue returned to the continuous extraction apparatus and extracted with anæsthetic ether during 4 or 5 hours.

The ethereal extract is passed through a small filter and the flask and filter washed with small quantities of the same solvent until a total volume of 120 ml. is obtained.

Half of the above ethereal solution is extracted successively with two 10-ml. portions, and then with two 5-ml. portions, of a 1 per cent. aqueous solution of tartaric acid. The mixed acid extracts are gently warmed in a current of air in order to remove dissolved ether, the liquid allowed to cool and diluted to 30 ml. with water. This solution will contain the total alkaloids, which are determined colorimetrically by mixing 1 ml. with 2 ml. of a solution containing 0·125 per cent. of *p*-dimethylaminobenzaldehyde in 65 per cent. by volume of sulphuric acid containing 0·005 per cent. of ferric chloride. The blue-violet colour produced, which attains its maximum intensity in 5 minutes and remains stable for some hours, is compared with that developed by similarly treating 1 ml. of a 0·006 per cent. solution of ergotoxine ethanesulphonate in 1 per cent. aqueous solution of tartaric acid. Each millilitre of this solution contains 0·05 mg. of ergotoxine base. The comparison may conveniently be made by transferring each coloured test mixture to a 1 cm. all-glass cell and measuring the colours with a Lovibond Tintometer (The British Drug Houses pattern), the measurement being made in terms of the Lovibond scale. Under these conditions the standard solution is matched by 4·1 units of blue and about 1·4 units of red. The blue units only are considered, it being assumed that the intensity of the blue component is directly proportional to the amount of alkaloid present. The colour produced by the sample under test should not differ from the standard by more than 20 per cent.; if the discrepancy exceeds this, it is necessary to repeat the colour test after suitably adjusting the volume of the tartaric acid solution containing the extracted alkaloids. The result is expressed as total alkaloids calculated as ergotoxine.

Fig. 5.—THE CHEMICAL ASSAY OF ERGOT (1)

Extracting the ethereal solution of the alkaloid with aqueous tartaric acid solution. It is customary to conduct alkaloidal assays in duplicate, and the illustration shows a set of separating funnels in use.

The remaining 60 ml. of the ethereal extract

is now shaken with successive 20-ml. portions of water, which have been rendered faintly alkaline with ammonia, until no further water-soluble alkaloids of ergot can be removed from the ether as shown by submitting 1 ml. of a separated aqueous extract to the colour test. The ethereal solution, from which the ergometrine has now been removed, is extracted with successive portions of 1 per cent. aqueous solution of tartaric acid, the dissolved ether removed from the combined extracts, the latter diluted to 30 ml. and the colour test applied as before.

By the above procedure the total alkaloids and the water-insoluble alkaloids are determined, both being calculated as ergotoxine. By subtraction the proportion of water-soluble alkaloids, calculated as ergotoxine, is obtained ; from this the proportion of water-soluble alkaloids, as ergometrine, is derived by multiplying by the factor 0·538. In this result any ergometrinine which may be present is included.

Another Method of Assay

An alternative procedure to the above has been proposed in which the tartaric acid solution containing the total alkaloids is adjusted to a reaction equivalent to pH 5·5, by the addition of disodium hydrogen phosphate solution, the mixture extracted with ether (when only the ergotoxine group of alkaloids are removed), the alkaloids in the ether again transferred to tartaric acid solution and the colour test applied while the aqueous solution, now freed from ergotoxine, is examined for its content of the water-soluble alkaloids ergometrine and ergometrinine. At the time of writing an analytical method for the separation of the two water-soluble alkaloids has not been fully developed, but an investigator in the United States, Donald C. Grove, has pointed out that ergometrine may readily be

Fig. 6. — THE CHEMICAL ASSAY OF ERGOT (2)

Weighing out the standard ergotoxine ethanesulphonate on an air-damped balance. As only a few milligrams of standard alkaloid are used it is essential to weigh with great accuracy. In this type of balance no rider is employed, the last 50 milligrams being read off directly on the illuminated scale to be seen inside the case at the top centre. Thus, in finishing the weighing, the instrument does not swing to and fro, but the beam sets in a position related to the difference in weight between the loads on the two pans.

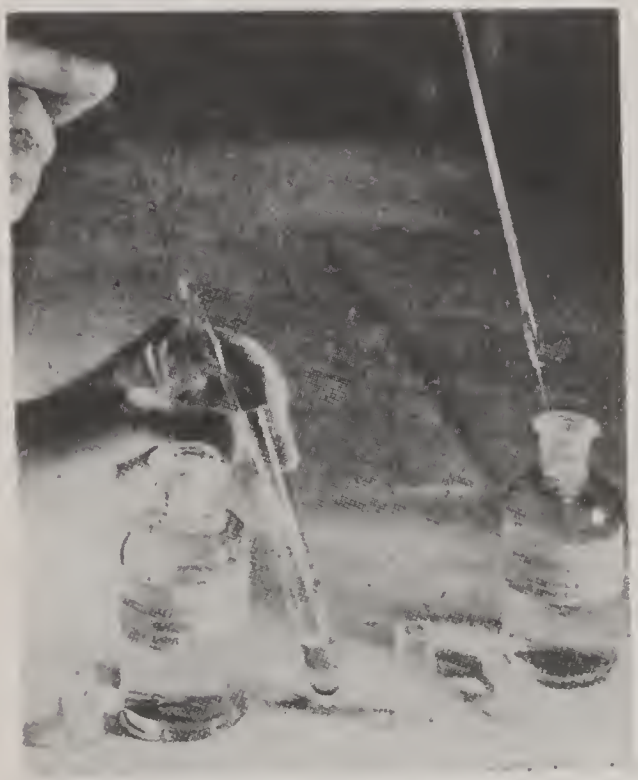


Fig. 7.—THE CHEMICAL ASSAY OF ERGOT (3)

Adding 2 ml. of the *p*-dimethylaminobenzaldehyde reagent to 1 ml. of the solution of the extracted alkaloids.

extracted from a slightly ammoniacal aqueous solution by shaking with successive portions of ether whereas, under the same conditions, almost the whole of any ergometrinine present remains in the aqueous layer.

Assay of Liquid Extract of Ergot

The following special procedure has been found satisfactory for removing the alkaloids of the water-soluble group as well as those belonging to the ergotoxine series. To 10 ml. of the galenical contained in a separator is added 7 ml. of a 20 per cent. aqueous solution of sodium hydroxide and 50 ml. of a saturated aqueous solution of sodium chloride. This is shaken with 50 ml. of a mixture of 3 volumes of ether and 1 volume of acetone and after separation the aqueous layer is drawn off into another separator and the extraction continued with 40-ml. portions of the mixed solvent until all alkaloidal material has been removed as indicated by applying the colour test to the residue remaining after evaporating a portion of a final ether-acetone extract. The alkaloids are now transferred to a 1 per cent. aqueous solution of tartaric acid

Fig. 8.—THE CHEMICAL ASSAY OF ERGOT (4)

Measuring the colour produced by the test using the Lovibond Tintometer (The British Drug Houses Pattern).

by shaking with successive small portions in the usual way and the dissolved solvents removed from the acid solution by submitting it to reduced pressure at room temperature for 1 hour. The subsequent determination of the total alkaloids and the separation of the alkaloidal groups is conducted on the lines already indicated in the description given above for the assay of ergot itself.

Chapter VI

NUX VOMICA, COCA, IPECACUANHA AND EPHEDRA

FOR descriptive purposes the majority of the alkaloidal drugs do not admit of any convenient mode of grouping, and the reader should understand that in this chapter, and the one to follow, the particular sequence adopted has no natural significance whatever.

NUX VOMICA

The drug consists of the dried ripe seeds of *Strychnos Nux-vomica*, a fair-sized tree indigenous to almost the whole of India. The fruit, about the shape and size of an orange, contains a soft, bitter pulp, in which are embedded the four or five disc-shaped seeds. The diameter of the seeds varies from 10 to 30 mm. and the thickness averages about 5 mm. The grey or greenish-grey surface has a silky appearance due to being covered with closely appressed hairs radiating from the centre. At one point on the margin the micropyle forms a prominence from which a raised line passes to the centre of the seed. The drug is odourless, but possesses an intensely bitter taste.

Chemistry of Nux Vomica

The principal constituents are the two alkaloids, strychnine and brucine, together with a small amount of the glucoside, loganin. It is stated that a trace of a third alkaloid, strychnicine, is also present. The percentage of total alkaloids varies from about 2 to 5 per cent., but is generally about 2·8 per cent. Of this, approximately one half is strychnine. The drug also contains caffeotannic acid and about 3 per cent. of fatty material. The physiological actions of brucine and strychnine are simi-

Fig. 1.—NUX VOMICA SEEDS
The average weight of these seeds is 30 grains, and each seed, therefore, contains approximately 1/5 of a grain of strychnine. In the absence of medical attention, the taking of two powdered seeds might well prove to be fatal.

lar, but, since the latter is about forty times more potent, it follows that it is by far the more important constituent of the drug.

The chemical constitution of strychnine is very complex and has not yet been finally settled, although its probable structural formula is known. The empirical formula is $C_{21}H_{22}O_2N_2$.

Assay of Nux Vomica

The evaluation of this drug aims firstly at the determination of the total alkaloids consisting almost entirely of a mixture of strychnine and brucine, and secondly, of the proportion of strychnine. The first determination is conducted by methods of extraction analogous to those already described for the alkaloidal drugs.

Determination of Total Alkaloids

Many modifications of general methods have been proposed for this assay and the following procedure has the merit of being convenient to apply.

The drug is finely powdered and 7·5 gm. is added to a flask containing 25 ml. of chloroform, 50 ml. of ether and 5 ml. of 10 per cent. ammonia solution. The mixture is shaken at frequent intervals during half an hour and then 50 ml. of the liquid is filtered through a pledget of cotton-wool and transferred to a separating funnel. Dilute sulphuric acid is added and the mixture well agitated. The lower aqueous layer, which should have an acid reaction when tested with litmus paper, is drawn off into a second separating funnel and the ether-chloroform liquid extracted twice or thrice more with dilute acid.

The mixed acid extractions, containing the alkaloids from 5 gm. of the original drug, are now rendered alkaline with dilute ammonia and the liberated alkaloidal bases completely extracted by shaking with several portions of chloroform.

The chloroform extractions, after being each washed in turn with a little water contained in a third separating funnel, are transferred to a tared flask, and the solvent recovered by distillation. A little alcohol is added and at once evaporated, and the residue, consisting of strychnine and brucine, is dried at 100° C. and weighed.

Determination of Strychnine

The process generally adopted for quantitatively separating strychnine from brucine depends upon the greater readiness with which brucine is nitrated by nitric acid. The method is empirical since time, temperature and acid concentration have to be so regulated that the alkaloidal properties of the brucine are completely destroyed, while the strychnine still

Fig. 2.—SEPARATION OF STRYCHNINE FROM BRUCINE

Concentrated nitric acid is added to a solution of the mixed alkaloids in dilute sulphuric acid. The nitric acid destroys the alkaloidal properties of the brucine, but, under the specified conditions, does not affect the strychnine which is subsequently extracted and weighed.

remains unaffected. Of the numerous variations of the method which have been suggested, the following is, perhaps, as suitable as any.

The total alkaloids are dissolved in 10 ml. of dilute sulphuric acid (10 per cent. by weight) by the aid of gentle warming, and the solution is filtered into a measuring cylinder and the flask and filter washed with water. When 50 ml. of filtrate has been collected, the temperature is adjusted to 25° C., and exactly 5 ml. of concentrated nitric acid is added and the liquid well mixed (Fig. 2). The addition of the nitric acid causes the pale straw solution of the alkaloids to assume instantly a brilliant crimson colour, a reaction characteristic of brucine. After standing for exactly 15 minutes, the liquid is transferred to a separating funnel, at once rendered alkaline with sodium hydroxide solution and the strychnine extracted with three or four portions of chloroform in the usual way. After removing most of the chloroform by distillation, a little alcohol is added and the evaporation to dryness completed. After drying at 100° C., the residue of strychnine is weighed. Alternatively, the alkaloid may be dissolved in an excess of decinormal sulphuric acid and titrated back with decinormal sodium hydroxide, using methyl red as indicator. Each ml. of decinormal acid is equivalent to 0·03342 gm. of strychnine.

This process is generally attributed to C. C. Keller, who, in 1893, defined the best conditions for its application; but the idea of nitrating brucine was first suggested by W. A. Shenstone in 1877.

Pharmacy of Nux Vomica

This drug is exceedingly valuable as a stimulating tonic. The liquid extract, which is used for making the tincture, is standardised to contain

1·5 per cent. of strychnine. It is prepared by exhausting the powdered seeds with 70 per cent. alcohol by percolation, evaporating the percolate to low bulk, and, while still hot, adding a proportion of hard paraffin, heating to 60° C., and shaking and allowing to cool. This treatment removes the fat naturally occurring in the seeds. The fat-free liquid is then poured off, diluted with alcohol, filtered, assayed for strychnine content, and the preparation adjusted to the correct strength.

Tincture of nux vomica, which is the galenical most frequently prescribed by doctors as an ingredient of tonic medicines, is prepared by diluting the liquid extract with alcohol and water so that the product contains 0·125 per cent. of strychnine. For administration in pills, either the standardised powdered drug (1·2 per cent. strychnine) or the dry extract, containing 5 per cent. of strychnine, is used.

Assay of Liquid Extract of Nux Vomica

This preparation may be assayed by transferring 10 ml. to a separating funnel, adding 25 ml. of dilute solution of ammonia and extracting with several portions of chloroform. The mixed chloroformic extracts are shaken with three successive portions of dilute acid, the chloroform being finally rejected and the acid extracts mixed and rendered alkaline with ammonia. The total alkaloid is then extracted again with chloroform, the latter removed and the dried mixed alkaloids treated by the nitration method for the separation of the strychnine.

STRYCHNINE

Strychnine itself is so extensively used in medicine, both as a tonic and as a vaso-constrictor in cases of cardiac failure, that a reference to its preparation should be included in any account of nux vomica.

Isolation of Strychnine

The coarsely powdered seeds are steamed under pressure in a

Fig. 3.—Colour reaction for strychnine

The alkaloid is dissolved in a drop of concentrated sulphuric acid and the solution touched with a trace of potassium dichromate. The presence of strychnine is revealed by the appearance of a transient violet-coloured streak.

boiler and the resulting magma is treated with milk of lime and hot solvent naphtha. After mechanical agitation with power-driven beaters, the naphtha is separated and the alkaloids extracted from it by shaking with just sufficient dilute sulphuric acid to neutralise the bases. The aqueous liquor is separated and cooled, when the strychnine sulphate crystallises out, whilst most of the brucine sulphate remains in solution. The crude strychnine sulphate is dissolved in water and the alkaloid liberated with sodium carbonate solution, collected, and recrystallised from alcohol until free from brucine. Strychnine occurs as colourless, rhombic prisms, very slightly soluble in water or ether, but readily dissolved by chloroform. Strychnine hydrochloride, which is the salt mostly used for medicinal purposes, is soluble in about 40 parts of water.

Colour Reaction for Strychnine

Besides yielding positive reactions with the usual alkaloidal tests, including Mayer's reagent and gold chloride solution, strychnine also gives a characteristic colour reaction. If a speck of the alkaloid is dissolved in a drop of concentrated sulphuric acid and the solution quickly stroked with a glass rod, to which a trace of finely powdered potassium dichromate is adhering, a transient deep violet coloured streak is produced (Fig. 3).

ST. IGNATIUS BEANS

Before leaving the subject of nux vomica, reference may be made to Ignatius beans, which are the seeds of *Strychnos ignatii*, a climbing plant indigenous to the Philippine Islands. The seeds, which are irregularly ovoid in shape, and measure about 25 mm. in length, contain about the same proportion of strychnine and brucine as nux vomica. The drug itself is very little used in medicine, but it is of some commercial importance as a source of strychnine.

COCA

Coca, "the divine plant of the Incas," has been cultivated in Peru and Bolivia for many centuries. The native Indians chew the dried leaves of the shrub after mixing them with slaked lime or plant ash, and thereby allay the onset of hunger and temporarily derive increased powers of physical endurance.

The leaves from three varieties of the plant are employed commercially. Truxillo, or Peruvian, coca originates from *Erythroxylum truxillense*, and consists of dried pale green leaves 3 to 6 cm. long and 2 to 3 cm. broad. The brownish-green Bolivian coca leaves, from *Erythroxylum coca*, may be 4 to 8 cm. long and 2·5 to 4 cm. broad, but smaller leaves are common.

On the upper surface of both varieties the midrib lies in a slight depression, while on the under surface two curved lines run from the base to the apex of the leaf on either side of the midrib. These features, which are quite obvious in the Bolivian drug, are not so strongly marked in the leaves of Truxillo coca.

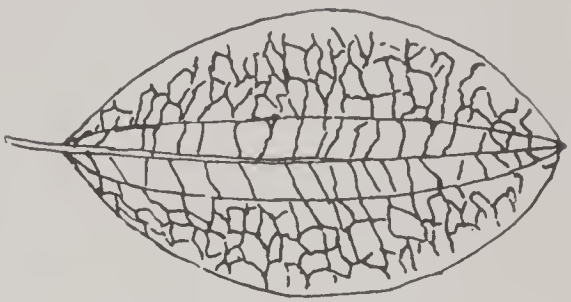


Fig. 4.—COCA LEAF

This shows the venation of the underside of the Bolivian leaf. Note the prominent lines on each side of the midrib.

When the epidermal cells of the under surface are examined microscopically they are seen to project in the form of papillæ, which in surface view appear as circular rings. This important diagnostic characteristic is illustrated in Fig. 5. *Erythroxylum coca* is also cultivated in Ceylon and Java. The plant used in the latter country is a special variety (*spruceanum*, Burck), and it is richer in alkaloid than the drug grown in other countries.

Chemistry of Coca

The leaves contain several alkaloids derived from ecgonine, the most important of which is cocaine. The other alkaloids include cinnamyl-cocaine, α-truxilline, β-truxilline, isatropyl-cocaine and benzoyl-ecgonine. The percentage of total alkaloids present in the commercial leaves varies from 0·1 to 2·4, Java coca containing the highest amount, consisting largely of cinnamyl-cocaine. Truxillo leaves generally contain more alkaloid than the Bolivian drug, but only about one-half is cocaine, whereas this alkaloid may constitute three-fourths of the total bases yielded by the material from Bolivia.

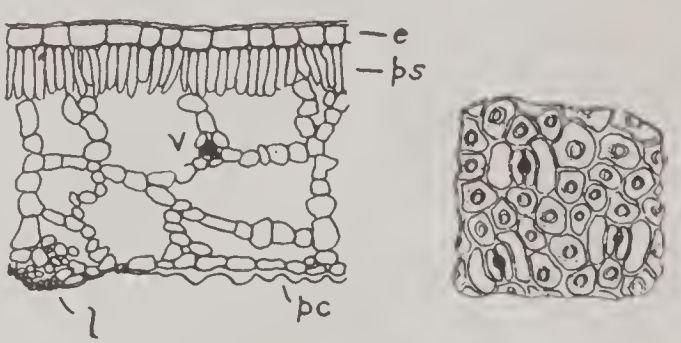
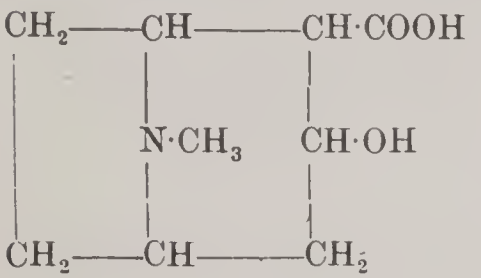


Fig. 5.—HISTOLOGICAL STRUCTURE OF COCA LEAF, HIGHLY MAGNIFIED

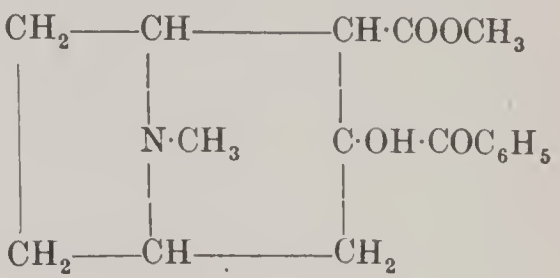
The left-hand diagram shows a transverse section of a Bolivian leaf: (e), upper epidermis of leaf; (ps), palisade cells; (v), veinlet; (l). line on under surface which runs alongside the midrib; (pc), papillose cells of lower epidermis. The right-hand figure is a surface view of the lower epidermis showing the papillose cells which appear under the microscope as circles. The dark structures are stomata.

When cocaine and the above-mentioned associated alkaloids are hydrolysed by heating with dilute hydrochloric acid they all yield ecgonine, which is a carboxylic acid derivative of

tropine, one of the hydrolytic products of atropine (see page 29). Cocaine itself is benzoyl-methylecgonine, and its relationship to ecgonine is clearly expressed in the following formulæ :—



ecgonine



cocaine

Another alkaloidal substance of some importance is found in coca, particularly in that from Java, called tropacocaine. On hydrolysis this forms benzoic acid and pseudo-tropine, a stereoisomeride of tropine.

Besides the alkaloidal constituents, the drug contains glucosidal substances and a tannin termed cocatannic acid, but these are of little relative significance.

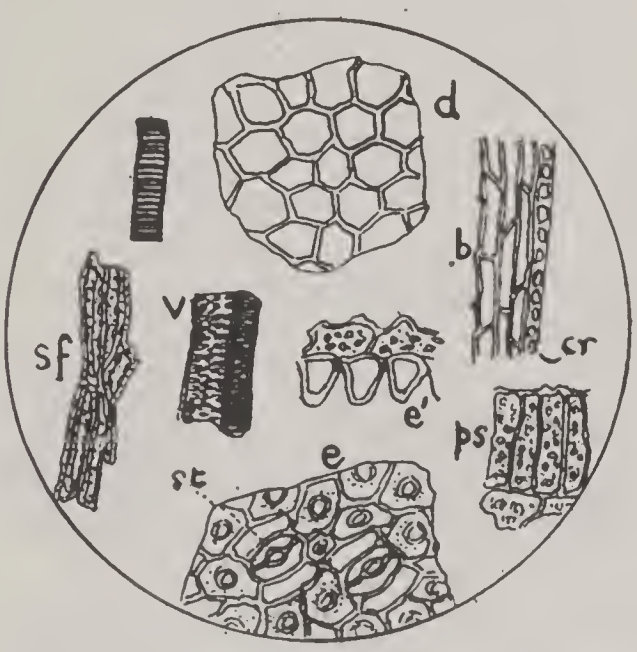


Fig. 6.—POWDERED COCA LEAF SHOWING ISOLATED HISTOLOGICAL ELEMENTS (× 240).

The characteristic papillose cells of the lower epidermis are shown at (e) in surface view and at (e′) in section; (st), stomata; (sf), sclerenchymatous fibres; (v) fragments of vessels from midrib; (d) upper epidermis; (b) bast; (cr), crystals of calcium oxalate; (ps), palisade cells.

Assay of Coca

The alkaloids contained in coca are soluble in petroleum ether, and this solvent may conveniently be used for the preliminary extraction. The assay can be conducted on the normal principles of extraction and need be indicated only in outline, since the details have already been sufficiently explained in previous accounts of alkaloid drugs.

Fifteen gm. of the powdered drug is macerated with 150 ml. of petroleum ether for 10 minutes, 1 ml. of dilute ammonia is then added, the mixture shaken at intervals during two hours, and the drug agglomerated by the addition of about 15 ml. of water. The supernatant liquor is filtered

through a plug of cotton-wool, 100 ml. (equivalent to 10 gm. of the drug) transferred to a separating funnel and extracted in the usual way with several portions of dilute hydrochloric acid. The acid extracts are washed with ether to remove fatty material, then mixed together and rendered alkaline with ammonia and the alkaloids extracted with ether. The alkaloidal residue left after evaporating the ether is dried at 80° C. and determined by dissolving in a measured volume of decinormal acid and titrating back with decinormal alkali, using methyl red as indicator.

Each ml. of decinormal acid is equivalent to 0·030318 gm. of total alkaloids calculated as cocaine.

Pharmacy of Coca

Galenicals made from the leaves were at one time used as stimulants during convalescence, but they are now rarely prescribed, owing to the grave risk of inducing a craving for the drug. The liquid extract is prepared by percolating powdered coca leaf with 60 per cent. alcohol, then evaporating the percolate to low bulk at a temperature not exceeding 80° C. The supernatant liquor is poured off from the precipitate which forms and the latter washed with water, the washings being added to the clear liquor; the strength of the preparation is then determined by alkaloidal assay and finally adjusted by further evaporation, or dilution with 60 per cent. alcohol. This preparation should contain 0·5 per cent. of total alkaloids.

One part of liquid extract, diluted to 6 parts with simple elixir, forms elixir of coca. Simple elixir consists of 40 parts of syrup and 7·5 parts of tincture of orange diluted with water to 100 parts. Coca wine is made by diluting 1 volume of elixir to 8 volumes with sherry which has been detannated by maceration with gelatin.

Coca Leaves from a Pre-Incan Grave

An interesting investigation was conducted in 1930 by C. Olive Griffiths on some coca leaves obtained from the pre-Incan necropolis of Nasca, situated in a desert 150 miles south-east of Lima, the capital of Peru. These leaves, which were in an excellent state of preservation, were contained in a small bag attached to the mummy pack, and there seems to be little doubt that they were deposited in the grave long before the beginning of the Christian era. The drug was found to contain traces of alkaloidal material, although the presence of cocaine itself could not be established. Histological examination of the leaves revealed that their cellular structure, even to the smallest details, was the same

as that found in the Peruvian variety growing to-day. Nature, in evolving her multitudinous species of living things, bides her time, and the millenniums of our antiquity "are but as an evening gone."

COCAINE

Coca is mainly employed as a source of cocaine, which, despite its numerous synthetic rivals, is still an important local anæsthetic. In order to save freightage and to eliminate the risk of deterioration to which the leaves are subject, the alkaloids are generally extracted in the country of origin and imported into Europe under the name of "crude cocaine." The greater part of the crude material used to-day is prepared in Java and largely consists of the cinnamyl derivative.

Isolation of Crude Cocaine

The dried and powdered leaves are mixed with about 5 per cent. of slaked lime and sufficient water to form a paste and the mixture is extracted with high-boiling petroleum at a temperature of 80° to 100° C. in an iron vessel provided with a steam jacket and stirring apparatus; after separation, the petroleum is agitated with dilute hydrochloric acid and the separated aqueous liquor is neutralised and evaporated to dryness, leaving a residue of alkaloidal hydrochloride. Alternatively, the acid liquid is rendered alkaline with sodium bicarbonate and the precipitated alkaloidal bases separated and dried.

Preparation of Pure Cocaine

The crude alkaloid is now hydrolysed to ecgonine by heating in an autoclave for an hour at 150° C. with a 0·2 per cent. excess of hydrochloric acid. On cooling, the liberated benzoic, cinnamic, and truxillic acids are removed by extracting with an organic solvent and the aqueous liquor evaporated to dryness, leaving impure ecgonine hydrochloride. Pseudo-tropine hydrochloride, derived from tropacocaine, may also be present. After washing the product with alcohol, the base is isolated by treatment with sodium carbonate and extraction, after drying, with hot alcohol, being finally purified by recrystallisation.

The purified ecgonine is now methylated by heating with methyl alcohol and hydrochloric acid, and the methyl-ecgonine is extracted with chloroform and purified by distillation under greatly reduced pressure. Finally, the methyl-ecgonine is converted to benzoyl-methyl-ecgonine (cocaine) by dissolving it in benzene and boiling the solution under a

reflux condenser with a slight excess of benzoyl chloride. The cocaine hydrochloride, which separates on cooling, is finally converted to the base by treatment with alkali and extraction with chloroform, and purified by recrystallisation from alcohol. The hydrochloride is then re-formed and further purified by recrystallisation from mixtures of alcohol and petroleum ether. In this manner all the alkaloids of coca, except tropacocaine, are converted into the medicinally important cocaine.

Properties of Cocaine and its Hydrochloride

Cocaine alkaloid occurs as colourless, odourless, monoclinic prisms which melt at 98° C. It is almost insoluble in water, but dissolves in oil and the common organic solvents. The taste is bitter and is followed by a sensation of tingling and numbness in the mouth.

In appearance the hydrochloride superficially resembles the base, and consists of an odourless crystalline powder or small transparent crystals. It is very soluble in water, but insoluble in oil and ether and slightly soluble in chloroform. When determining the melting point the capillary containing the sample should not be inserted in the heating bath until the temperature has attained 193° C.; under these conditions cocaine hydrochloride melts at 197° to 199° C.

Tests for Cocaine

One of the most characteristic tests for cocaine is the formation of violet rectangular plates on treatment with potassium permanganate solution. About 0·1 gm. of the base is dissolved in just sufficient decinormal hydrochloric acid to form a neutral solution, a little alum solution is added, followed by 1 per cent. aqueous potassium permanganate; on stirring, the characteristic violet crystals are formed, which are easily seen under the microscope.

The absence of isatropyl-cocaine in cocaine hydrochloride is confirmed by dissolving 0·1 gm. in 100 ml. of water, adding a trace of ammonia, and scratching the sides of the containing vessel with a glass rod. A crystalline precipitate of cocaine should be produced, while the supernatant liquor remains free from turbidity. This is known as Maclagan's test. An acidified aqueous solution should not readily decolorise when treated with a drop of dilute potassium permanganate, thus indicating the absence of cinnamyl-cocaine.

Pharmacy of Cocaine

The drug is mainly employed in surgical and dental practice to produce localised anæsthesia, for which purpose sterile solutions of the

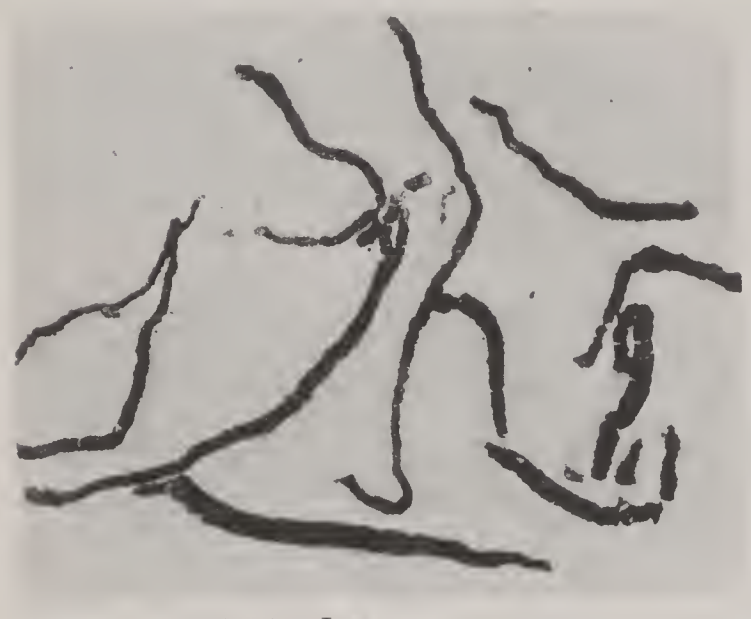


Fig. 7.—IPECACUANHA ROOT

This shows a specimen of the typical Brazilian drug. It is imported in bales weighing about 1 cwt.

hydrochloride are generally most convenient; these often contain a trace of adrenaline hydrochloride in order to constrict the capillaries at the site of injection and thereby prevent rapid distribution of the anæsthetic which otherwise occurs. When cocaine is administered orally it excites the central nervous system and induces a sense of exhilaration and an increased capacity for physical work.

Gelatin eye discs, containing 1/50 of a grain of the hydrochloride, and an eye ointment, consisting of 0·25 per cent. of the same salt in a basis of yellow soft paraffin containing 10 per cent. of wool fat, are both important galenicals for ophthalmic use.

Cocaine hydrochloride is a constituent of the official lozenge of krameria and cocaine, which is a most valuable medicine for the relief of severe coughs due to irritant conditions of the throat. The preparation of this galenical is described in the account of krameria (see page 210).

Fig. 8.—VARIETIES AND SUBSTITUTES FOR IPECACUANHA ROOT

A, Genuine Brazilian root; B, Cartagena ipecacuanha; C, Undulated ipecacuanha (*Richardsonia sp.*); D, Lesser striated ipecacuanha (*Richardsonia sp.*); E, Greater striated ipecacuanha (*Psychotria emetica*). The three latter substitutes do not contain any emetine or cephaëline.

IPECACUANHA

The root of *Cephaëlis Ipecacuanha* is a highly important drug, being at once an emetic, a diaphoretic, one of the most convenient of the known expectorants, and an excellent remedy for the treat-

ment of amœbic dysentery. The root, which is derived from a small plant found in Brazil, especially in the provinces of Matto Grosso and Minas, occurs in commerce as dark brown, slender, tortuous, annulated rods about 15 cm. long and approximately 5 mm. in diameter (Fig. 7). Genuine ipecacuanha is also cultivated in the Straits Settlements. Cartagena ipecacuanha is an inferior variety grown in Colombia and frequently imported into this country ; it may be distinguished by its larger size and the more widely separated annulations. Several substitutes for the genuine drug have from time to time been offered in the market, but, being devoid of the characteristic alkaloids, they are quite worthless (Fig. 8).

Chemistry of Ipecacuanha

The root contains from 2 to 3 per cent. of total alkaloidal material consisting of the three substances emetine, $C_{29}H_{40}O_4N_2$, cephaëline, $C_{28}H_{38}O_4N_2$, and psychotrine. The alkaloids from genuine Brazilian or Indian (Johore) ipecacuanha consist of 60 to 70 per cent. emetine and 28 to 38 per cent. cephaëline, while psychotrine constitutes the remainder. Cephaëline is a phenolic body (containing the hydroxyl radicle OH) while emetine is the methoxyl derivative and is consequently non-phenolic. Although cephaëline is a powerful emetic, it is ineffective as an expectorant and its presence in excessive amount is undesirable. Cartagena ipecacuanha contains about the same proportion of total alkaloids as the Rio variety, but as only about 40 per cent. is emetine, it should not be employed for the preparation of galenicals.

Assay of Ipecacuanha

The evaluation of this drug involves a determination of the total alkaloids and also the proportion of non-phenolic bases (mostly emetine). The following process is one of the simplest.

To determine the total alkaloids the root is powdered and 7 gm. treated with 70 ml. of a mixture of chloroform 1 vol. and ether 3 vols. After 5 minutes, 5 ml. of 10 per cent. ammonia solution is added, the mixture shaken at intervals during one hour and the drug then agglomerated by the addition of about 5 ml. of water. Fifty ml. of the clear supernatant liquid is transferred to a separating funnel and extracted by shaking with several portions of dilute hydrochloric acid. The mixed acid extracts are rendered alkaline with ammonia and the liberated alkaloids extracted with chloroform, each chloroformic extraction being washed in succession with about 10 ml. of water contained in a second separating funnel. The chloroform is removed by distillation, a little alcohol added and at once evaporated and the residue dried at 100° C. for 5 minutes. The alkaloidal residue is dissolved in an excess of decinormal sulphuric acid and the

solution titrated back with decinormal sodium hydroxide using methyl red as indicator. Each ml. of decinormal acid is equivalent to 0·0240 gm. of total alkaloid, calculated as emetine.

In order to determine the non-phenolic alkaloids the above titration liquid is transferred to a separating funnel, rendered alkaline with sodium hydroxide solution and shaken with about 50 ml. of ether. The separated ethereal solution is agitated successively with two portions of very dilute aqueous sodium hydroxide, these alkaline shakings then added to the main aqueous solution and the mixed alkaline liquid extracted with further portions of ether. The mixed ethereal solutions are washed with successive quantities of about 10 ml. of water until free from alkali, each of the aqueous washings being shaken in turn with a single portion of ether contained in another separating funnel. All the ethereal liquids are transferred to a flask, the ether evaporated, and the amount of alkaloidal residue determined by adding an excess of decinormal acid and titrating back with decinormal alkali using methyl red as indicator, the result being calculated as emetine.

This procedure effects a separation of the cephaëline, which, being phenolic, forms a salt with the sodium hydroxide, and is thus left in the aqueous liquor when the emetine is extracted with ether. Genuine ipecacuanha should contain non-phenolic alkaloids equivalent to not less than three-fifths of the total.

Assay of the Galenicals

The liquid extract of ipecacuanha may be assayed by transferring 10 ml. to a separating funnel, acidifying with dilute mineral acid, removing non-alkaloidal extractive matter by shaking with several portions of chloroform and, after rendering alkaline with ammonia, extracting the alkaloids with chloroform in the usual way and titrating the residue. The separation of the non-phenolic alkaloids is then conducted by treating the titration liquid by the method already described. When dealing with the more dilute galenicals, larger volumes are taken and evaporated to low bulk before commencing the extraction.

The Pharmacy of Ipecacuanha

Preparations made from the whole drug are particularly useful as expectorants in the treatment of bronchitis and whooping cough. The liquid extract, which is standardised to contain 2 per cent. of total alkaloids, is made by the standard percolation process with 90 per cent. alcohol (see page 8). It is principally used for making the weaker galenicals which are more suitable for prescribing.

Ipecacuanha wine consists of a 5 per cent. by volume solution of the liquid extract in sherry, the mixture being filtered after standing for

48 hours. It should contain 0·1 per cent. of total alkaloids but, in practice, some alkaloidal material is carried down by the precipitate which forms when the liquid extract is mixed with the wine.

In the present British Pharmacopœia the time-honoured ipecacuanha wine has been replaced by a tincture made by diluting 5 vols. of the liquid extract to 100 vols. with alcohol, glycerin and water ; it contains about 22 per cent. of alcohol. The dose for the purpose of an expectorant is 10 to 30 minims, while, if a fluid ounce be administered, the preparation acts as an emetic in the course of about half an hour.

Vinegar of ipecacuanha is considered by some physicians to be a more effective expectorant than the wine and is made by diluting 5 vols. of the liquid extract with 10 vols. of 90 per cent. alcohol and 85 vols. of 5 per cent. acetic acid.

Compound powder of ipecacuanha is a useful diaphoretic for the treatment of colds and consists of 10 per cent. each of powdered ipecacuanha root and opium, with a suitable diluent such as potassium sulphate or lactose. This is the Dover's powder referred to on page 21 ; many different formulæ for the preparation have been tried, but all contain ipecacuanha and opium as the essential ingredients.

Lozenge of morphine and ipecacuanha is an excellent remedy for severe coughs and is made by adding powdered ipecacuanha root and morphine hydrochloride to sucrose and gum acacia, both in fine powder, adding a little tincture of tolu and making into a paste with water. After cutting, the lozenges are dried in a hot-air chamber. Each lozenge should contain 1/10 of a grain of ipecacuanha and 1/32 of a grain of morphine hydrochloride.

EMETINE

In order to isolate the alkaloid from powdered ipecacuanha, the root is extracted with alcohol, the combined extracts acidified with hydrochloric acid, the alcohol distilled off and the residue diluted with water. The separated fat and non-alcoholic extractive material is filtered off, the filtrate rendered alkaline with ammonia and the alkaloids extracted with chloroform or ether. The cephaëline is removed by agitating the organic solution of the mixed alkaloids with aqueous sodium hydroxide, the emetine then extracted with hydrobromic acid and the emetine hydrobromide carefully recrystallised. The hydrochloride can be prepared by regenerating the base and, after separation, neutralising it with hydrochloric acid and recrystallising the salt.

The cephaëline separated by the sodium hydroxide solution may be converted to emetine by adding sodium bicarbonate to the alkaline liquid, extracting with chloroform, converting the base to its hydrochloride and purifying by recrystallisation. The cephaëline is then regenerated with sodium carbonate, extracted with chloroform, and the dried

chloroformic extract of cephaëline alkaloid dissolved in a solution of sodium metal in fusel oil, sodium methyl sulphate added, and the cephaëline methylated by boiling the mixture under a reflux condenser. The resulting emetine is then extracted with diluted hydrochloric acid and purified by recrystallisation, any unchanged cephaëline being removed by treatment with sodium hydroxide.

Characteristics of Emetine and its Salts

Emetine base occurs as an amorphous white powder which becomes yellow on storage. When a trace of emetine is dissolved in a few drops of concentrated hydrochloric acid and a little hydrogen peroxide added to the solution, a deep yellowish-pink colour is produced. The hydrochloride, $C_{29}H_{40}O_4N_2.2HCl.7H_2O$, is a colourless, odourless crystalline powder, readily soluble in water. If a small quantity of the hydrochloride is added to a very dilute solution of molybdic acid in concentrated sulphuric acid, a bright green colour is produced. This reaction serves as an identity test.

Emetine bismuth iodide is a reddish-orange powder which is insoluble in water and alcohol, but is dissolved by acetone. Strong acids and alkaline solutions decompose the salt.

Treatment of Amœbic Dysentery

There are two principal varieties of dysentery, that known as bacillary being due to the *Bacillus dysenteriæ* (of Shiga or of Flexner), and the amœbic form caused by a protozoa called *Entamœba histolytica* (Fig. 9). The latter disease, which is very common in all tropical countries, is well treated by ipecacuanha. The administration of the root itself is attended with difficulties owing to its emetic properties, and it is now customary to give emetine hydrochloride by injection or to administer the insoluble emetine bismuth iodide orally.

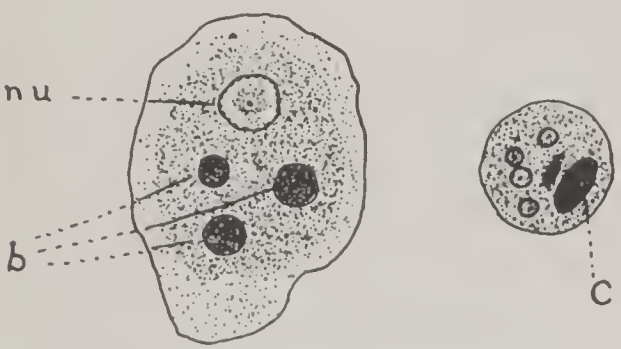


Fig. 9.—ENTAMŒBA HISTOLYTICA

The protozoa responsible for amœbic dysentery, magnified over 1000 diameters. The left-hand drawing shows the motile life stage; *nu*, the nucleus with peripheral chromatin granules and central karyosome; *b*, ingested red blood corpuscles. The right-hand drawing depicts the encysted non-motile life stage with four nuclei and the chromatoid body marked C. Before encystment, contained food is ejected.

Of the several species of parasitic amœbæ liable to inhabit the human intestines, *Entamœba histolytica* is the only one that is pathogenic.

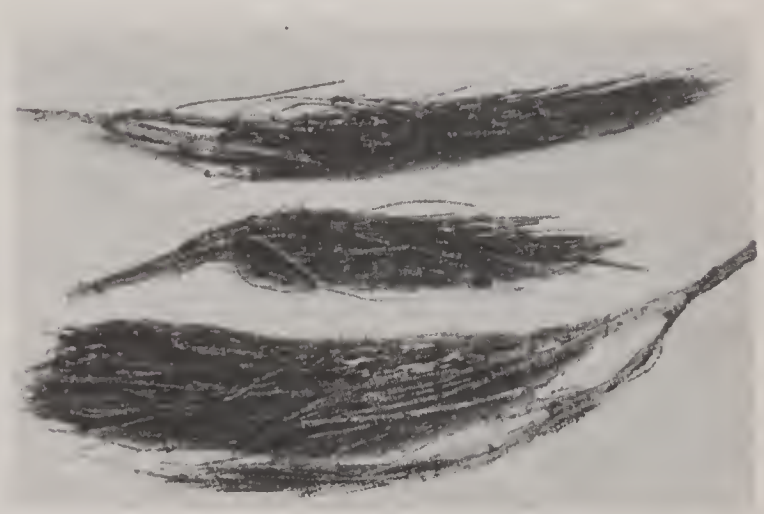


Fig. 10.—Chinese ephedra

This drug is imported in bales weighing from 2½ to 4 cwt.

Its diet consists almost entirely of red blood corpuscles and it secretes a ferment capable of dissolving the mucous membrane of the large intestine thus enabling it to reach the submucosa and then extend its excavations laterally beneath the surface, forming typical flask-shaped ulcers. During an acute attack of dysentery swarms of amœbæ can be found in the stools, which consist mainly of a purulent mixture of blood and mucus ; the intestinal actions, accompanied by intense pain, often take place every few minutes. Treatment of this condition by emetine rapidly destroys the majority of the amœbæ, not only giving merciful relief to the patient but preventing almost inevitable death. The liability to further acute attacks generally remains, and it seems probable that a few of the organisms frequently manage to escape the action of the drug, possibly by finding refuge in pockets of the intestinal walls.

ACALYPHA

This is an Indian drug and is used as a substitute for ipecacuanha. The entire herb is employed, the active constituents being a resin and an alkaloid, acalyphine. Taken in moderate amounts the drug is an expectorant, while it possesses some laxative action and is emetic in large doses. It is variously administered in the form of tincture, decoction and infusion, while the fresh herb is used in the preparation of Succus Acalyphæ, the juice being expressed, one-third of its volume of alcohol added, the mixture allowed to stand for 7 days and then filtered.

EPHEDRA

Ephedra, or Ma Huang, is said to have been employed medicinally by the Chinese 5000 years ago, but it has only become prominent in Western medical practice during the last 20 years. Owing to its value in the treatment of asthma, it is now a drug of considerable importance.

Fig. 11.—EPHEDRA

In this drawing the pairs of opposite rudimentary leaves at each node are clearly represented.

The ephedra of commerce consists of the dried young branches of various species, including *Ephedra sinica* and of *E. equisetina*, natives of China, and of *E. Gerardiana* and *E. nebrodensis*, both indigenous to India. The drug consists of switches of thin, sub-cylindrical, green stalks, arising from stouter brown woody branches which in their turn are attached to still thicker stems. The green stalks vary from 7 to 30 cm. in length and may be about 2 mm. in diameter at their thickest part; they are characterised by bearing diminutive leaves in opposite pairs at intervals of about 4 cm. (Fig. 11).

Botanical Classification of Ephedra

Ephedra occupies a position of peculiar interest in the general classification of the vegetable kingdom, since it belongs to one of the three genera which constitute the class of Gymnosperms called Gnetales. The Gymnosperms, in which the seeds are situated on an open scale instead of being provided with a seed vessel as in the true flowering plants, or Angiosperms, are the smallest division of the vegetable kingdom, embracing only 14 per cent. of the known species, as compared with 59 per cent. belonging to the Angiosperms. Although the Gymnosperms include the Conifers and may seem abundant in some areas, yet when the whole world is considered the Angiosperms are unquestionably the dominant division, growing in the utmost profusion and capable of adapting themselves to mountainous regions of perpetual snow or to the almost rainless wilderness of African deserts. In untold ages past, from the end of the Carboniferous to the beginning of the Cretaceous era, the Gymnosperms were the pre-eminent flora and the most highly organised plants of the world.

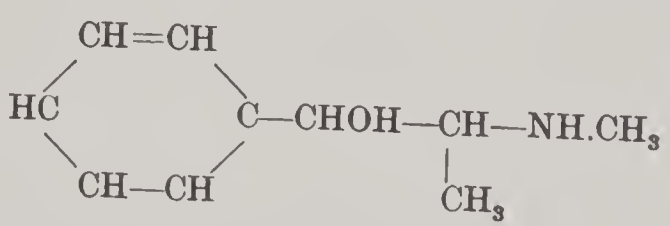
It is therefore interesting to observe that ephedra belongs to a very small class of Gymnosperms, revealing in their structure marked resemblances to the Angiosperms and thus possibly being near relatives of those transitional types that must have existed during the Cretaceous period to herald the advent of the true flower. Since then the whole of the Tertiary cycle of the world's history has come and gone and during the passage of that unimaginable time the pride of the Gymnosperms has faded and the flowering plants have become undisputed lords of the vegetable kingdom.

TABLE V—CLASSIFICATION OF THE GYMNOSPERMS, SHOWING THE POSITION OF EPHEDRA

Class	*Living or Extinct*	*Principal Representative*	*Remarks*
Pteridospermæ	Extinct ..	Lyginodendron	Possessed characters intermediate between the Ferns and Cycads. Extinct before the commencement of the Mesozoic era.
Cycadales ..	About 100 species still living	Cycas	Superficial resemblance to palms ; live 1000 years or more. Possess the largest motile spermatozoids known in any living organism.
Bennettitales	Extinct ..	Dacotensis and Gibsonianus (Luccombe Chine fossil)	Possessed many points of resemblance to the Angiosperms.
Ginkgoales ..	One species still living	Maidenhair tree	Cultivated in gardens in the East. Dicecious and has motile spermatozoids.
Cordaitales ..	Extinct ..	Cordaites ..	Possibly forerunners of the Conifers.
Coniferales ..	Living ..	Pines, cypresses, yews	Largest class of Gymnosperms. Spermatozoids non-motile.
Gnetales ..	About 40 species living : 35 belonging to Ephedra	Ephedra ..	Anatomy of this class shows close resemblances to the structure of Angiosperms.

Chemistry of Ephedra

The physiologically active principles are the alkaloids ephedrine and its stereoisomeride pseudo-ephedrine. The graphical formula for ephedrine is :—



and it is seen that, for an alkaloid, its structure is relatively simple. When isolated and purified it occurs as a deliquescent white crystalline solid freely soluble in water and melting between 38° and 42° C. Small quantities of the N-methyl derivative of both ephedrine and pseudo-ephedrine are also present in the drug. The total alkaloidal content varies between about 1 and 2 per cent., of which 60 to 70 per cent. is ephedrine.

Test for Ephedrine

Unlike the majority of alkaloids, ephedrine does not yield any precipitate when its acid solutions are treated with Mayer's reagent. If a solution of a few milligrams of the alkaloid or of one of its salts in 1 ml. of water is treated with a drop of copper sulphate solution followed by about 1 ml. of sodium hydroxide solution, a violet colour is produced. When this liquid is shaken with a little ether and the immiscible liquids allowed to separate, the ethereal layer is coloured purple and the underlying aqueous portion becomes blue.

If ephedrine is dissolved in chloroform and the solution allowed to stand for some hours, the base is converted into the hydrochloride and crystals of this salt separate as a crystalline precipitate. This test distinguishes ephedrine from pseudo-ephedrine.

Assay of Ephedra

The process for the evaluation of this drug follows on the general lines for the determination of alkaloidal content, but certain special details of technique must be observed. Since the alkaloids are freely soluble in water it is necessary to saturate the alkaline aqueous extracts with sodium chloride before shaking out with ether. Again, ephedrine base is very readily volatilised when warmed, and it is therefore necessary to avoid evaporating its ethereal solutions to dryness on the water-bath. The separation of ephedrine from pseudo-ephedrine may be accomplished by treating the mixed hydrochlorides with chloroform, in which ephedrine hydrochloride is insoluble.

Determination of Total Alkaloids

The drug is powdered and 20 gm. is macerated for a few minutes with 200 ml. of a mixture of 3 volumes of ether and 1 volume of chloroform. About 10 ml. of 10 per cent. ammonia solution and 1 gm. of anhydrous sodium carbonate are added and, after shaking frequently during 4 hours, the mixture is allowed to stand overnight. It is then transferred to a percolator and extracted, first with 100 ml. of the ether-chloroform mixture, then with ether itself until all alkaloid has been removed. The colour test already described may be applied to a few drops of the percolate to ascertain when the drug is exhausted. The percolate is transferred to a separating funnel and shaken with four successive portions of dilute hydrochloric acid ; the acid shakings are mixed together, filtered, and the filter washed with a little more dilute acid. The filtrate is nearly neutralised with sodium hydroxide solution, transferred to a separating funnel, 10 gm. of anhydrous sodium carbonate and sufficient sodium chloride to saturate the liquid are added, and the mixture is shaken until the solids are dissolved. The aqueous solution is

extracted with five separate portions of ether, the separated and combined ether extracts allowed to stand until clear, and then decanted through a pleated filter into a beaker. The ethereal solution of the alkaloids is warmed and poured off into a flask from crystals of sodium chloride, which usually separate at this stage. The bulk of the ether is distilled off and the remainder allowed to evaporate spontaneously without the application of heat. The alkaloidal residue is dissolved in excess of decinormal sulphuric acid, the solution diluted with a little water and titrated with decinormal sodium hydroxide using methyl red as indicator. Each millilitre of decinormal acid is equivalent to 0·01651 gm. of total alkaloids calculated as ephedrine.

Determination of Ephedrine Hydrochloride

The alkaloidal liquid, after being titrated, is transferred to a separating funnel, rendered alkaline with sodium carbonate and saturated with sodium chloride. The alkaloids are extracted with several portions of ether, and the latter evaporated to low bulk. The alkaloids in the ethereal solution are then precipitated as hydrochlorides by rendering just acid to litmus paper with an alcoholic solution of hydrogen chloride gas. This acid liquid should be introduced from a capillary tube, the ether being well agitated in the meantime, thus avoiding the addition of more than the slightest excess of acid. The precipitated alkaloidal hydrochlorides are filtered off on a sintered glass crucible, washed with a saturated ethereal solution of ephedrine hydrochloride, and dried at 80° C. The ephedrine hydrochloride is separated from the pseudo-ephedrine hydrochloride by macerating the dried mixture with dry chloroform, which dissolves the latter salt, and collecting the insoluble ephedrine hydrochloride in a tared Gooch crucible, drying at 80° C., and weighing.

EPHEDRINE

The isolated alkaloidal salts are almost exclusively used in medicine in preference to preparations made directly from the whole drug. Ephedrine hydrochloride, which is official in the British Pharmacopœia 1932, occurs as odourless, colourless crystals, soluble in water forming a neutral solution.

Isolation of Ephedrine Hydrochloride

The extraction of the alkaloids on a large scale may be conducted by macerating the powdered drug with 0·5 per cent. aqueous solution of hydrochloric acid for several hours and then pressing out the liquor and extracting the marc a second time with more acid. The mixed extracts are filtered, neutralised with sodium carbonate, evaporated to low bulk, and then rendered strongly alkaline with sodium carbonate and the mixture

again filtered. The filtrate is saturated with sodium chloride, the alkaloids extracted with ether, and most of the solvent removed by distillation. The concentrated ethereal solution is carefully acidified with an alcoholic solution of hydrogen chloride, the precipitated alkaloidal hydrochlorides filtered off, and dried. The pseudo-ephedrine hydrochloride is removed by treatment with dry chloroform, leaving the ephedrine hydrochloride, which may be further purified by recrystallisation from alcohol.

Pharmacology of Ephedrine

The physiological action of ephedrine resembles that of adrenaline, with the additional advantages that, unlike the latter, it can be administered orally and its effects are more prolonged. About 1 gr. of ephedrine hydrochloride, given by the mouth, produces an increase in blood-pressure with decreased rate of heart-beat lasting for approximately 2 hours. Like adrenaline it will dilate the pupils and has been successfully employed in ophthalmological work. A 1 per cent. solution of ephedrine alkaloid in light paraffin forms a useful spray for the alleviation of hay fever.

As an alternative to injections of adrenaline, ephedrine is most valuable for relieving the spasms of asthma. The spasmodic attacks suffered by asthmatic persons are due to the muscles of the bronchioles contracting and thus reducing the cross-sectional area of the membranes which divide the blood capillaries from the chambers of air intake. This condition causes acute distress, since it is across these membranes that the exchange by diffusion of oxygen and carbon dioxide takes place between the inbreathed air and the blood. The administration of ephedrine effectively relaxes the muscles of the bronchioles and thus affords rapid relief.

Chapter VII

ALKALOIDAL DRUGS OF SUBSIDIARY IMPORTANCE

AS already indicated at the commencement of the previous chapter, convenience of presentation is the principal reason for assembling the descriptions of this group of alkaloidal drugs together. Of the eight medicaments about to be discussed perhaps jaborandi is the most important, although each finds valuable, if limited, application in medicine.

JABORANDI OR PILOCARPUS

This drug is but little employed in the form of preparations of the crude drug, it having been found more satisfactory to utilise the isolated alkaloid pilocarpine, which is the active constituent. *Pilocarpus jaborandi* is a shrub, indigenous to Brazil, which produces compound leaves. The drug consists principally of the dull brownish-grey leaflets which vary in length from 6 to 10 cm. Several substitutes for *Pilocarpus jaborandi* are available, of which *P. microphyllus*, illustrated in Fig. 1, is the most important, since it is the principal commercial source of the alkaloid pilocarpine. The leaflets of this plant do not exceed 4 cm. in length.

Fig. 1.—JABORANDI LEAVES

The picture shows the variety called *Pilocarpus microphyllus*, which is the most important commercial source of the alkaloid pilocarpine.

Chemistry of Jaborandi

Jaborandi contains three alkaloids termed pilocarpine, isopilocarpine, and pilocarpidine. The proportion of total alkaloid varies from about 0·5 to 1 per cent., and a good specimen of *P. microphyllus* will contain

quite 0·5 per cent. of pilocarpine, $C_{11}H_{16}O_2N_2$. Isopilocarpine is isomeric with pilocarpine, but its physiological activity is much less.

Assay of Jaborandi

The proportion of total alkaloids may be determined by the method employed for belladonna (see page 29), excepting that the initial percolation should be conducted with chloroform instead of ether. In calculating the result from the final titration, each ml. of fiftieth normal acid is equivalent to 0·004163 gm. of total alkaloid calculated as pilocarpine.

PILOCARPINE

To obtain the alkaloid the powdered jaborandi leaves are exhausted with hot alcohol, the alcohol removed by distillation, the residue dissolved in ammoniacal alcohol and the solution filtered. Most of the alcohol is again removed, and the residue poured into hot 1 per cent. hydrochloric acid and the liquid allowed to stand some days to allow resins to precipitate. After filtration the liquid is rendered alkaline with ammonia and the alkaloid extracted with chloroform. The chloroform is distilled off and the residual pilocarpine converted at once into the nitrate by dissolving in a small quantity of alcohol and rendering the solution just acid with very dilute nitric acid. The solution is seeded with a crystal of previously prepared pilocarpine nitrate, when the main bulk of the dissolved salt slowly crystallises. The product is recrystallised from alcohol.

Properties of Pilocarpine and its Salts

The alkaloid itself is a colourless, thick syrupy liquid, easily soluble in water, alcohol, or chloroform. The nitrate, which is the salt most generally employed in medicine, occurs as colourless crystals, or as a white crystalline powder, soluble in about 8 parts of water, but almost insoluble in ether or chloroform.

Colour Reaction for Pilocarpine

The identity of pilocarpine may be established by dissolving about 20 mg. of the base or one of its salts in 5 ml. of extremely dilute sulphuric acid, adding a few drops of hydrogen peroxide solution, followed by 1 ml. of benzene, and a drop of potassium chromate solution. After shaking and allowing to separate, the benzene will be coloured deep bluish-violet, while the aqueous layer remains yellow.

Medicinal Uses of Pilocarpine

Pilocarpine, in the form of a sterile aqueous solution of the nitrate, is administered by hypodermic injection as a powerful diaphoretic,

especially in renal dropsy and in uræmia. It also finds employment in the treatment of epilepsy. In ophthalmic surgery, pilocarpine nitrate is used to contract the pupil and to reduce intra-ocular pressure in glaucoma. The physiological action of this alkaloid is in all respects opposite to that of atropine.

CALABAR BEANS OR PHYSOSTIGMA

This consists of the seeds of *Physostigma venenosum*, a plant resembling the common scarlet runner, but having a woody stem and climbing to a height of 50 ft. or more. It is indigenous to the West Coast of Africa and flourishes around the lower reaches of the Niger and the Old Calabar River. It is sometimes termed the "ordeal bean" from the former practice of the pagan tribes of Western Africa, who compelled persons accused of witchcraft to swallow one of these very poisonous seeds. If, after the administration of a crushed bean mixed with water, the suspected person succumbed, his guilt was considered proved.

Fig. 2.—CALABAR BEANS

These are also called "ordeal beans" from the former practice of certain native African tribes in making persons accused of witchcraft undergo the often fatal punishment of swallowing the powder derived from one of the crushed seeds. They contain the alkaloid physostigmine.

The chocolate-brown, odourless, almost tasteless seeds average about 25 mm. in length and 12 mm. in thickness. In plan, the seeds are reniform, being almost flat on one side and curved on the other. A deep groove runs along the curved side and passes round one end of the seed. The outer seed coat is hard and thick.

Chemistry of Calabar Bean

The chief constituent is the alkaloid physostigmine, $C_{15}H_{21}O_2N_3$. This compound, which is also called eserine, occurs to the extent of 0·15 to 0·3 per cent. Traces of two other alkaloids, called eseridine and eseramine, are also present. Like jaborandi, calabar bean is rarely used in the form of preparations made from the whole drug and it is, therefore, appropriate to refer to the isolation of physostigmine.

PHYSOSTIGMINE

This alkaloid readily oxidises on exposure to air, and it is, therefore, customary to prepare the salicylate, which is the most stable salt, without attempting to isolate the free base. The crushed beans are exhausted with 90 per cent. alcohol and, after removal of the alcohol from the resulting extract, the hot residue is poured into 0·1 per cent. sulphuric acid, the mixture meanwhile being violently agitated. After cooling, the separated fat is filtered off, the clear solution rendered alkaline with sodium bicarbonate and extracted with ether. The ethereal solution is evaporated to low bulk, extracted with dilute sulphuric acid, the separated aqueous solution neutralised and mixed with an excess of sodium salicylate. The physostigmine salicylate which separates out is purified by crystallisation from alcohol and dried *in vacuo*.

Properties of Physostigmine Salicylate

This salt, which is the one commercially used, occurs as colourless or faintly yellow crystals, which gradually acquire a red tint on exposure to air and light. It is soluble in about 100 parts of water. On adding a little dilute sodium hydroxide to an aqueous solution a white precipitate is produced which turns pink ; this is soluble in excess of sodium hydroxide forming a red solution.

Medicinal Uses of Physostigmine

This alkaloid induces myosis of the pupils, similarly to pilocarpine, and is employed for the same purposes. When injected, it stimulates the peripheral nerve-endings and thereby increases gastric movement and peristalsis, and for these reasons it is employed in veterinary practice as a hypodermic purgative. As in the case of pilocarpine the action of physostigmine is antagonised by atropine.

HYDRASTIS

Hydrastis canadensis, or golden seal, is a small plant widely distributed over Canada and the eastern United States. The rhizome, which is the portion of the plant used medicinally, occurs as small twisted yellowish-brown pieces about 3 cm. in length. Each piece bears several short upright branches, each exhibiting a cup-shaped scar left by an aerial stem, while numerous rootlets also remain attached to the rhizome.

Chemistry of Hydrastis

The most important constituent is the alkaloid hydrastine, $C_{21}H_{21}O_6N$, which occurs in the proportion of 1·5 to 3 per cent. There is also present

about 3 per cent. of berberine, $C_{20}H_{17}O_4N$, and traces of a third alkaloid termed canadine. Isolated berberine occurs as a brown powder or, when highly purified, as brilliant yellow needles, and it is this constituent which is responsible for the colour of hydrastis rhizome.

Assay of Hydrastis

Most of the methods proposed for the assay of this drug aim at a simple determination of the ether-soluble alkaloids. In effect, the results represent the proportion of hydrastine, since berberine is almost insoluble in that solvent. The following process is convenient :—

To 6 gm. of the powdered drug in a dry flask is added 180 ml. of ether and, after 10 minutes, this is followed by 5 ml. of dilute ammonia. After occasional shaking during 2 hours, 5 ml. of water is added to agglomerate the drug and 150 ml. of the clear ethereal solution is poured into a flask and the ether removed by distillation. The residue is dissolved in dilute hydrochloric acid, the solution filtered into a separating funnel, and the flask and filter washed with more dilute acid. After rendering alkaline with ammonia and adding 40 ml. of ether, the mixture is shaken for 2 minutes; then 35 ml. of petroleum ether is added and the separating funnel is again agitated.

Fig. 3.—HYDRASTIS RHIZOME

This is also called golden seal—a name referring to its characteristic yellow colour which is due to the alkaloid berberine contained in the rhizome.

The ethereal liquid is now cleared by adding 1·5 gm. of powdered tragacanth, and 60 ml. is decanted into a tared flask, the ether removed, and the residue of hydrastine (derived from 4 gm. of the original drug) dried at 80° C. and weighed.

Uses of Hydrastis

The use of this drug is on the decline. It was at one time considered

to be of value for the arrest of internal hæmorrhage, but its action is uncertain. It has also found some employment as a bitter tonic, particularly in the treatment of gastro-intestinal catarrh. The tincture, liquid extract and dry extract are the usual galenicals, but their preparation does not call for special comment. The tincture, diluted with 4 volumes of water, is sometimes used as an astringent lotion.

Fig. 4.—European aconite root

Aconitum Napellus. The roots usually vary from 5 to 10 cm. in length, while the upper end may be about 2 cm. in diameter. It contains the exceedingly poisonous alkaloid aconitine.

ACONITE

Aconitum Napellus is a perennial herb which grows wild in Central Europe and is cultivated in England as a garden plant and, commercially, for its medicinal qualities. The plant is often called monkshood, in allusion to the cowl-shaped posterior sepal of its blue flower, while the popular name, wolfsbane, refers to its use on the Continent for poisoning meat bait intended for the destruction of wolves. The root, which is the part of the plant used medicinally, consists of dark brown longitudinally wrinkled conical pieces crowned by an aerial stem (Fig. 4). Another species of aconite which is grown in Japan, *Aconitum uncinatum*, var. *japonicum*, is now extensively employed in place of the European species (Fig. 5). The drug has a slight taste, which is followed by a characteristic sensation of tingling and numbness, lasting for some time.

Fig. 5.—Japanese aconite root

These roots are generally smaller than the European species. It contains the alkaloid japaconitine, which closely resembles, but is not identical with, aconitine.

Chemistry of Aconite

Three alkaloids are known to occur in the drug, of which the most important is the crystalline substance aconitine (acetyl-benzoyl-aconine), $C_{34}H_{47}O_{11}N$. Aconitine is intensely poisonous and even 1/300th of a grain taken orally is sufficient to induce distinct symptoms in man. The other alkaloids are amorphous, piraconitine (benzoyl-aconine) being much less toxic than aconitine, while aconine has little physiological action. The amorphous alkaloids are insoluble in ether, but aconitine dissolves readily. The proportion of aconitine in the European drug ranges from 0·2 to 0·5 per cent. The Japanese root is stated to contain japaconitine, an alkaloid closely resembling aconitine, but not identical with it. The total alkaloidal content of this species is somewhat higher than that of *Aconitum Napellus*.

Assay of Aconite

The total alkaloids may be determined by the method described for the assay of gelsemium (see page 88), each millilitre of fiftieth normal acid being equivalent to 0·01291 gm. of alkaloid calculated as aconitine. However, clinicians prefer to use material standardised on its actual physiological potency since the character of the alkaloidal material is complex and inclined to vary considerably according to the source of the drug. The United States Pharmacopœia includes a biological assay in which the lethal effect of the sample is tested with guinea pigs. This authority directs that the potency of aconite shall be such that the equivalent of 0·1 gm., in the form of a 1 in 10 tincture made by the percolation process, shall be equivalent to not less than 0·15 mg. of a standard aconitine alkaloid which is distributed by the U.S.P. Board of Trustees. The dose of the sample is directed to be so adjusted that it kills not more than 7 and not less than 3 animals of groups of 10 within 6 hours.

Pharmacy of Aconite

Owing to its high toxicity and the abundance of alternative synthetic drugs, the use of aconite is declining. Small doses of the tincture are sometimes employed as a febrifuge in treating the common cold, tonsillitis, and allied disorders. Liniment of aconite, which may be regarded as a 1 in 2 liquid extract containing 3 per cent. of camphor, is used as an external application for the treatment of neuralgia and acute rheumatism.

GELSEMIUM

The yellow jasmin, *Gelsemium nitidum*, is a climbing plant indigenous to the southern United States; it should not be confused with the entirely different yellow-flowering jasmin cultivated in Britain. The

rhizome and root, which constitutes the drug, consists of purplish-brown, approximately cylindrical pieces about 15 cm. long and 0·5 to 2 cm. in diameter, to which rootlets and aerial stems are attached. The purple colour is produced by a network of lines, the intervening areas being yellowish-brown.

Chemistry of Gelsemium

The drug contains from 0·2 to 0·7 per cent. of alkaloidal material consisting of at least two substances, namely gelsemine, obtainable in crystalline form, and gelseminine. which is apparently amorphous and possesses much greater physiological potency than gelsemine. Besides the alkaloids, gelsemium root contains β-methyl-æsculin, which exhibits an intense bluish-green fluorescence in alkaline solution; æsculin itself is a fluorescent substance which occurs in the bark of the horse chestnut tree. The drug also contains about 6 per cent. of fixed oil and approximately 4 per cent. of resinous material.

Fig. 6.—Gelsemium Rhizome

The illustration shows both aerial stems and roots attached to the pieces. The rhizomes are hard and woody. The drug has a bitter taste and a slight aromatic odour.

Assay of Gelsemium

Preparations containing 0·1 per cent. or more of the alkaloids of gelsemium are included in the First Schedule of the Poisons Rules, 1935. The following method for the assay of the root is essentially that recommended by the Poisons Sub-Committee of the Society of Public Analysts.

The drug is reduced to No. 60 powder, 10 gm. mixed with 5 gm. of acid-washed sand and the mixture macerated with 100 ml. of a mixed solvent consisting of 3 volumes of ether and 1 volume of chloroform. After the elapse of 10 minutes, 5 ml. of dilute ammonia solution is added, the whole shaken at intervals during 1 hour and then transferred to a percolator. The extraction is continued with the same mixed solvent until the alkaloid is completely removed. The percolate is tested for complete extraction by separately collecting about 2 ml. in a dish, evaporating the solvent, dissolving the residue in a few drops of decinormal sulphuric acid and adding 1 drop of decinormal iodine; the presence of

the alkaloids of gelsemium is indicated by the formation of a brown precipitate. The percolate is transferred to a separating funnel and extracted, first with 30 ml. of normal sulphuric acid, then with several 10-ml. portions of decinormal sulphuric acid. The mixed acid solutions are washed with 10 ml. of chloroform, the latter being shaken in another separating funnel with 20 ml. of decinormal sulphuric acid, then rejected. The two acid liquids are combined, neutralised with dilute ammonia solution and 2 ml. of the latter added in excess. The alkaloids are then extracted by shaking with successive 20-ml. quantities of chloroform, each extract washed with the same 20 ml. of water contained in another separating funnel, and then transferred to a flask. The solvent is distilled off, 2 ml. of absolute alcohol added to the residue, the latter removed by evaporation and the residue dried at 60° C. for 30 minutes. The alkaloidal material is dissolved in 2 ml. of alcohol (95 per cent.), 10 ml. of fiftieth normal acid added and the excess titrated with fiftieth normal sodium hydroxide using methyl red as indicator. Each millilitre of acid is equivalent to 0·00732 gm. of alkaloids calculated as gelsemine.

Uses of Gelsemium

The drug is mainly employed in association with the bromides and tincture of cimicifuga as an analgesic in the treatment of neuralgia, toothache, and rheumatism ; but owing to its liability to produce disturbances of vision and other symptoms of poisoning, it is not very generally prescribed, although in some cases it has been found useful for the treatment of severe influenza. Gelsemium has been omitted from the British Pharmacopœia 1932, but the drug and tincture were included in the previous edition (1914). Tincture of gelsemium is a 1 in 10 preparation made with 60 per cent. alcohol by the standard percolation process.

COLCHICUM

The autumn crocus or meadow saffron (*Colchicum autumnale*) is used as a specific remedy for gout. The plant is distributed over Europe and is common in England. Both the dried corm and seeds are employed in the preparation of galenicals. The corm occurs in commerce cut into greyish-white slices about 3 mm. thick and approximately 1·5 cm. in diameter. The hard, dull, nearly spherical reddish-brown seeds are about 2·5 mm. in diameter. Both the dried corm and seeds are odourless, but have a bitter taste.

Chemistry of Colchicum

The physiologically active constituent of colchicum is the pale yellow, amorphous, highly toxic alkaloid colchicine, $C_{22}H_{25}O_6N$, of which the

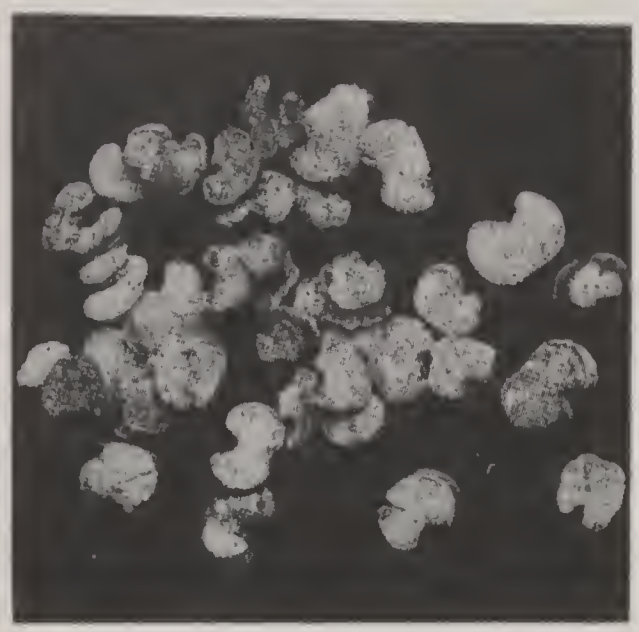


Fig. 7.—Colchicum corm (sliced)

This is a specimen of material grown and prepared in England.

corm contains from 0·2 to 0·6 per cent. and the seeds 0·2 to 0·8 per cent. Colchicine is soluble in water and in the common organic solvents. Its acid solutions do not yield any reaction with Mayer's reagent (potassio-mercuric iodide solution), but a brown precipitate is produced by a dilute solution of iodine in aqueous potassium iodide.

Assay of Colchicum

Although colchicine is soluble in water it is still possible to extract it from alkaline aqueous solution by agitation with chloroform, since the alkaloid dissolves even more readily in the organic solvent. The following process is applicable to both the corm and seeds.

Fifteen gm. of the powdered drug is digested with 10 ml. of lead subacetate solution and 290 ml. of water at 60°–70° C. under a reflux condenser. After 3 hours the mixture is filtered and 200 ml. of the filtrate treated with 0·75 gm. of dibasic sodium phosphate and shaken at frequent intervals during 30 minutes. The mixture is again filtered and 100 ml. of the filtrate (equivalent to 5 gm. of colchicum) transferred to a separating funnel and the alkaloid extracted by shaking with several portions of chloroform. In order to ascertain when extraction is complete a few drops of the chloroformic extract should be evaporated to dryness on a watch glass, any residue dissolved in a little dilute hydrochloric acid and the liquid tested for colchicine by adding a solution of iodine in aqueous potassium iodide ; the presence of colchicine will be indicated by the formation of a brown precipitate.

When all the colchicine has been removed from the aqueous layer the chloroformic extract is transferred to a tared flask, the solvent distilled off, and the residue treated with 1 ml. of alcohol, the latter at once evaporated, more alcohol then added and evaporated off and the residue dried at 100° C. and weighed. The residue consists of colchicine and a trace of resin, the proportion of which is determined by adding 10 ml. of water, filtering the resulting solution through a pledget of cotton-wool, washing the wool free from colchicine, dissolving the insoluble resin in alcohol, evaporating to dryness in a tared dish and weighing

after drying at 100° C. The weight of the resin deducted from the first weight gives the weight of colchicine in 5 gm. of the drug.

Pharmacy of Colchicum

Colchicum relieves pain and inflammation due to gout and is frequently prescribed in association with purgative drugs. Its continual use is liable to cause derangement of the central nervous system and it is necessary to exercise caution in its administration.

The dry extract, for use in pills, is made from the corm by the standard percolation process, using 60 per cent. alcohol. The percolate is evaporated under reduced pressure at a temperature not exceeding 60° C. and is standardised to contain 1 per cent. of colchicine.

The liquid extract, used for making tincture of colchicum, is prepared by the standard percolation method with 60 per cent. alcohol from the powdered and defatted seeds. It should contain 0·3 per cent. of colchicine. The tincture is made by diluting the liquid extract to ten times its volume with 60 per cent. alcohol, allowing to stand for at least 12 hours, and filtering.

Colchicum wine is prepared by macerating 20 parts of the powdered corm with 100 parts of sherry for 7 days, straining, pressing the marc, mixing the liquids obtained, and filtering. Colchicum wine is frequently prescribed with antacids and saline purgatives.

Colchicine and Tumours

For some time an inter-relationship has been suspected between the action of colchicine and mitosis (indirect nuclear division) following on the discovery of mitotic figures in the hæmopoietic, or blood-making, organs of normal healthy animals, and also in the neoplastic tissues of tumours, after the administration of colchicine. Preliminary experiments have been conducted by E. C. Amoroso, which indicate that injections of colchicine are capable of effecting the dispersal of tumours, and it is announced that further work in the treatment of these maladies with colchicine in association with X-rays and with radium is being pursued.

LOBELIA

This drug consists of the whole, dried, flowering plant of *Lobelia inflata*, or Indian tobacco, an annual herb indigenous to the eastern United States. The angular yellow or purplish stems average about 30 cm. in length. As seen in commerce the leaves are much broken and inconspicuous, but the two-celled capsular fruits are abundant. The drug possesses a slightly irritating odour and a burning acrid taste. When the stem of the growing plant is wounded a milky juice exudes

Fig. 8.—Lobelia

The numerous capsular fruits are easily seen, but the leaves are shrivelled. It is imported in bales weighing from $1\frac{3}{4}$ to $2\frac{1}{2}$ cwt.

which is contained in the laticiferous vessels which ramify throughout both stem and leaves (Fig. 9).

Chemistry of Lobelia

The principal physiologically active constituent of the drug is the dextrorotatory alkaloid lobeline, $C_{23}H_{29}O_2N$, which crystallises in broad colourless needles melting at 130° to 131° C. A second alkaloid termed lobelidine, $C_{20}H_{25}O_2N$, has also been isolated. The separation of these two alkaloids has been effected by repeatedly extracting an aqueous solution of the mixed hydrochlorides with chloroform, which removes the lobeline but not the lobelidine. Lobeline forms well-defined crystallised salts. The total alkaloidal content of the drug is stated to vary between 0·2 and 0·7 per cent.

Assay of Lobelia

The assay of this drug is of importance since preparations containing 0·5 per cent. or more of the alkaloids of lobelia are included in the First Schedule of the Poisons Rules, 1935. The following procedure is that recommended by the Poisons Sub-Committee of the Society of Public Analysts appointed to investigate methods of assay for various substances controlled by the above enactment.

The drug is reduced to No. 60 powder, 10 gm. mixed with 10 gm. of ignited sand and the mixture macerated with 75 ml. of a mixed solvent consisting of 4 volumes of ether and 1 volume of alcohol (95 per cent.). After the elapse of 15 minutes, 5 ml. of dilute ammonia solution is added, the whole shaken at intervals during 1 hour and then transferred to a percolator. The extraction of the drug is continued, first with 25 ml. of the ether-alcohol mixture and then with ether until the alkaloid is completely removed. The percolate is transferred to a separating funnel and extracted, first with 30 ml. of semi-normal sulphuric acid and 5 ml. of alcohol (95 per cent.) and finally with three further quantities of 20 ml. of the acid-alcohol mixture. The mixed acid solutions are washed,

first with 10 ml. and then with successive quantities of 5 ml. of chloroform, each chloroformic solution being washed with the same 20-ml. portion of semi-normal sulphuric acid contained in another separating funnel. The chloroform is rejected, the acid liquids mixed, neutralised with dilute ammonia solution and 5 ml. of the latter added in excess. The alkaloids are then extracted by shaking with successive 10-ml. quantities of chloroform, the extracts combined and washed with a little water, then filtered into a flask. The solvent is distilled until about 2 ml. of liquid remains, then 2 ml. of absolute alcohol is added and the evaporation completed; the residue is similarly treated with two further portions of absolute alcohol and then dried at 80° C. The dry alkaloidal material is dissolved in 2 ml. of alcohol (95 per cent.), 10 ml. of fiftieth normal acid added, and the excess titrated with fiftieth normal sodium hydroxide, using methyl red as indicator. Each millilitre of acid is equivalent to 0·00674 gm. of alkaloids calculated as lobeline.

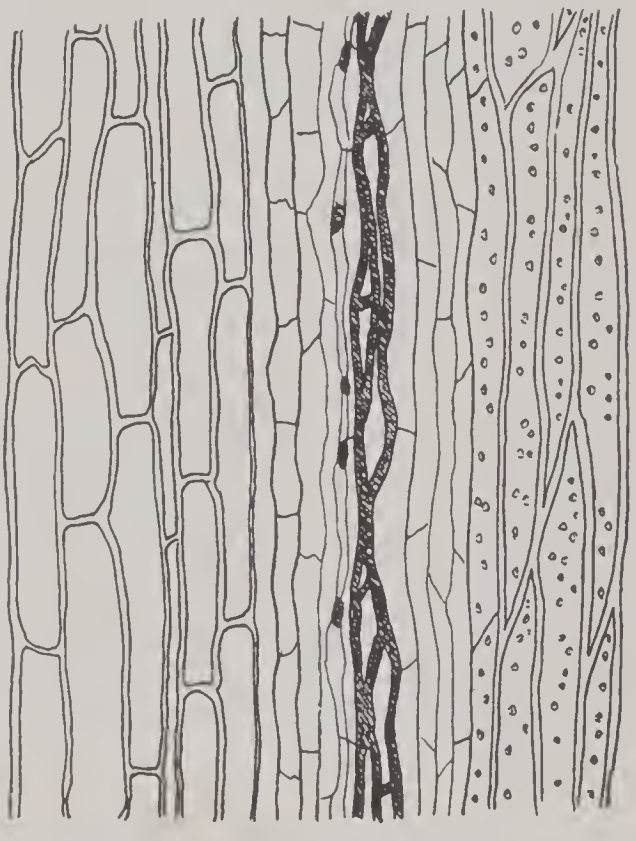


Fig. 9.—MAGNIFIED DIAGRAMMATIC DRAWING OF A RADIAL SECTION OF LOBELIA STEM

The dark tube-like structures are the laticiferous vessels which anastomose with one another, forming characteristic tissue elements which can be readily isolated from the rest of the plant by digesting with potassium hydroxide solution. Immediately to the right of the laticiferous vessels are the bast and cambium, and to the left the endodermis. The large cells on the extreme left compose the cortex, while the pitted cells on the right constitute the woody tissue.

Assay of Galenical Preparations

The evaluation follows on similar lines to the method described for the crude drug. A measured quantity is introduced into a separating funnel, acidified with dilute sulphuric acid, and vegetable extractive material removed by shaking with ether, the latter being rejected after washing with a portion of dilute acid contained in another separating funnel. After adding the acid washing to the main bulk of the aqueous liquor in the first separating funnel, and rendering the mixture alkaline with

ammonia, the alkaloid is extracted with ether and the assay completed as already indicated for the powdered drug. For the assay of weak tinctures, 100 ml. or more should be evaporated to low bulk before commencing the extraction.

Pharmacy of Lobelia

Preparations of lobelia are employed in the treatment of asthma although its use is now declining. Lobeline itself has a physiological action resembling that of nicotine ; it first excites nerve cells and then paralyses them.

Compound lobelia powder contains 25 per cent. each of lobelia, stramonium, tea leaves, and potassium nitrate together with a trace of oil of anise. The fumes produced by its burning are inhaled for the relief of asthma.

Ethereal tincture of lobelia is a 1 in 5 preparation made by percolating the powdered drug with spirit of ether (ether 1 vol., alcohol 2 vols.). This is employed as an antispasmodic and expectorant for the treatment of bronchitic asthma. The simple tincture of lobelia is made with 60 per cent. alcohol by the standard percolation process (see page 10) and is also used for asthmatic complaints.

CONIUM OR HEMLOCK

The spotted hemlock, *Conium maculatum*, grows wild in Great Britain and throughout temperate Europe and Asia. It is to be found as a handsome herb, 1 to 2 metres high, growing on hedge banks and near the borders of fields. The hollow, smooth, greenish stems are marked with dark purple spots, and when the plant is crushed it emits a disagreeable odour similar to that associated with mice. The dried material of commerce consists of ill-defined greyish-green pieces of plant material which do not admit of precise description. The ripe fruits are yellow but

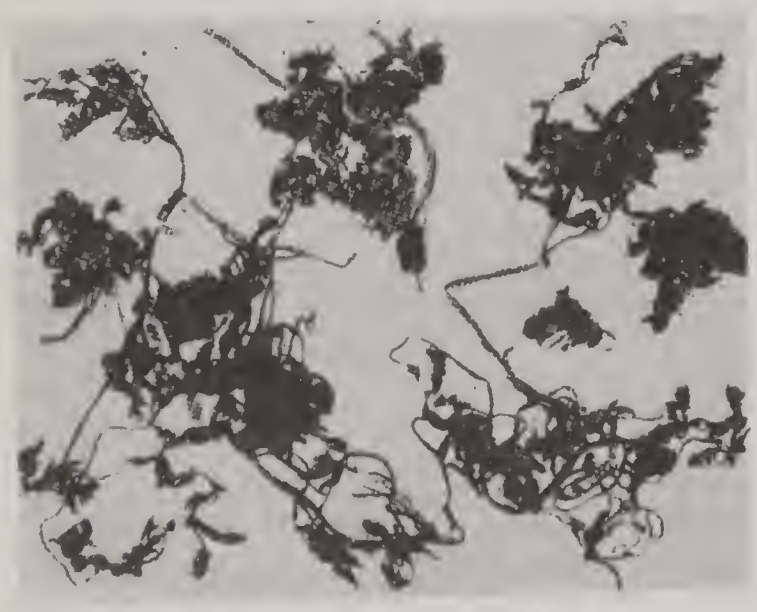


Fig. 10.—CONIUM HERB

This shows the dried material. Many of the galenicals were made from the fresh herb. Owing to its uncertain action the drug is now rarely prescribed.

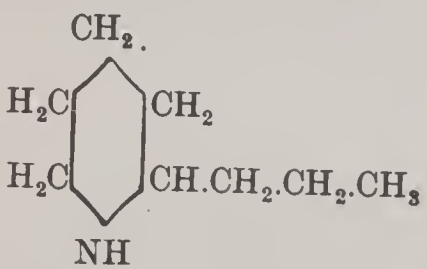
for medicinal purposes they should be gathered while still green; they occur as longitudinally fissured ovoid bodies about 3 mm. long, and in commercial specimens the mericarps (half fruits) are usually separated.

Fig. 11.—Conium or hemlock

This shows the form of the plant when growing. Note the characteristic spots on the stem. The drawing of the fruit is on a much larger scale than that of the whole plant. The fruits are only about 3 mm. long, but the plant may reach a height of 2 metres.

Chemistry of Conium

The drug contains the alkaloids coniine, γ-coniceine, conhydrine, methyl-coniine, and pseudo-conhydrine. Coniine was the first alkaloidal substance to be synthesised. Its constitution may be represented by the formula :—



The herb, apart from the fruits, contains approximately 0·2 per cent. of total alkaloids while the fruit often yields upwards of 2 per cent.

Assay of Conium

Coniine is a liquid alkaloid which readily volatilises when warmed, and in order to determine the alkaloidal content of the drug it is best to convert the extracted bases to the hydrochlorides and to weigh the salts. Pure coniine hydrochloride occurs as colourless crystals melting at about 212° C. The following process of assay is convenient :—

Five gm. of the dried and powdered fruit (or 25 gm. of the whole herb) is extracted for 2 hours in a Soxhlet apparatus (see page 124) with a solvent consisting of chloroform 5 vols., absolute alcohol 3 vols., and a saturated solution of hydrogen chloride gas in chloroform 2 vols. The cooled extract is transferred to a separating funnel, shaken with three portions of water, and the separated aqueous layers washed in turn with successive portions of chloroform. The chloroform washings are rejected, the

aqueous layers bulked, made alkaline with sodium hydroxide, and extracted with several portions of chloroform. The chloroformic solution of the alkaloidal bases is transferred to a tared flask, rendered just acid by the addition, from a capillary tube, of an ethereal solution of hydrogen chloride gas, the solvent then distilled, and the residue of alkaloidal hydrochlorides dried at 80° C. and weighed.

Pharmacy of Conium

Conium possesses a depressant action on the motor nerves and was at one time employed in the treatment of chorea and mania, while as an antispasmodic it has been tried in cases of whooping cough and asthma. The drug is mentioned in Anglo-Saxon medical literature and during the nineteenth century was much employed by physicians, but, owing to its uncertain action, it is now rarely administered internally. Coniine hydrobromide dissolved in a gelato-glycerin base is occasionally used as an external application for hæmorrhoids. The British Pharmacopœia of 1885 included both the whole herb and the fruit besides six galenicals prepared from them. The number of preparations was curtailed in the next issue (1898), and the drug finally omitted altogether in the Pharmacopœia of 1914.

Toxicology of Conium

As a poison the drug is specially interesting owing to the expressed juice of the fresh plant having been chosen by the ancient Greeks as the instrument of capital punishment, Socrates having been an illustrious victim. The practice has been described as a humane custom, on the supposition that death following the draught of hemlock juice is painless, and judging from the available toxicological evidence there would seem to be some justification for this statement. The symptoms of a fatal dose generally commence with dizziness and weakness of the legs, which after some hours deepens into paralysis of all the limbs accompanied by stupor and slight convulsions ; then the light fades, the enfeebled respiration fails and the life of the victim glides to infinitude.

Chapter VIII

GLUCOSIDAL DRUGS : HEART STIMULANTS

THE group now to be considered comprises digitalis, strophanthus and squill, which are by far the most valuable members of the glucosidal series. When administered, these drugs stimulate the beating of the heart, at the same time slowing the pulse rate, and are therefore of paramount importance in many forms of heart disease. No synthetic drugs capable of replacing the vegetable products have been discovered ; a few other herbs, such as convallaria, contain glucosides which act similarly, but they have not yet been sufficiently studied to justify their general clinical application.

DIGITALIS

The official drug consists of the leaves of the purple foxglove or *Digitalis purpurea*, a plant widely distributed throughout Europe and too well known to need description.

Chemistry of Digitalis

There is much confusion in regard to the identity of the active principles. The leaves contain several therapeutically active glucosides, of which two, digitoxin and gitoxin (0·2 to 0·4 per cent.), have been obtained in a pure crystalline state. The other glucosides have not been isolated as pure substances ; they occur as a mixture of closely related compounds termed amorphous digitalin. Digitoxin, often termed crystalline digitalin, is the most toxic constituent of the plant and is generally administered orally in the form of granules, while for the manufacture of hypodermic tablets and injection solutions amorphous digitalin is used.

Isolation of Digitalin

The amorphous glucosides may be isolated by treating a cold water percolate of the powdered leaves with lead acetate, which precipitates protein and other extractive matter, and, after filtering, removing the excess of lead acetate by precipitation with sodium carbonate and sodium phosphate and again filtering. The digitalin in the filtrate is then precipitated by adding tannic acid, and the moist precipitate of glucosidal tannate is mixed with litharge and powdered animal charcoal and then dried. The digitalin is dissolved from this mass by extraction with ethyl alcohol and, after removing the solvent by distilla-

tion, the residue is washed with a little water and again dissolved in alcohol, filtered, and the alcohol evaporated off a second time. The residue is extracted with chloroform and the solution filtered, and, on distilling off the chloroform, the digitalin is obtained as a cream or yellow amorphous powder. The yield may be about 0·5 per cent.

Digoxin

The leaf of another species of this drug, *Digitalis lanata*, is three to four times as potent as *D. purpurea* and is now used as a source for the manufacture of the crystalline glucosides. Besides digitoxin and gitoxin this species contains digoxin which is included in the Fourth Addendum to the British Pharmacopœia. Each glucoside exists in the leaf in combination with dextrose, and an acetyl group forming respectively the complex glucosides, digilanid A, B and C. Digoxin has some advantage over digitalin in that it acts more quickly and is therefore of more value in urgent cases of severe heart attack.

Colour Reactions of the Glucosides

Digitalin dissolves in concentrated sulphuric acid, giving a golden-yellow solution which changes to blood red ; if a drop of ferric chloride solution be added to the acid solution before it has turned red a brilliant purple coloration is produced.

Digitoxin does not produce a colour in sulphuric acid, but if it is dissolved in acetic acid containing a little ferric sulphate and the solution carefully layered on to sulphuric acid also containing ferric sulphate, an intense blue colour slowly develops at the zone of contact between the two layers. This reaction is not given by the other glucosides of digitalis.

Pharmacy of Digitalis

Although digitalin and digoxin are obtainable in commerce, most physicians find that for many purposes galenical preparations of the drug are more satisfactory. The British Pharmacopœia describes a standardised powdered leaf, a standardised tincture and a fresh infusion which must be prepared from standardised powdered leaf. These preparations are made by methods which have already been described, subject to modifications necessitated by the requirement that they are to be of specified potency.

Standardisation of Digitalis

Many attempts have been made to devise a chemical method for measuring the physiological activity of digitalis, but so far without

success. In the past, preparations of this drug were not officially required to pass any tests indicative of their activity, but the present British Pharmacopœia demands that they shall be biologically assayed, thereby ensuring that the public may always be served with digitalis of real therapeutic value. Before the issue of the last revision of the Pharmacopœia the larger wholesale drug firms had issued unofficial preparations of guaranteed potency to meet the vital need for standardised digitalis. The biological assay may be conducted by comparing the minimum quantity of the drug, which will kill 6 out of 12 frogs, with the minimum dose of a standard digitalis leaf, which effects the same result. Each frog must receive a dose proportionate to its weight.

The standard preparation is a mixture of powdered digitalis leaves which is kept in sealed vials at the National Institute for Medical Research, Hampstead, London. The international unit of activity is that contained in 0·08 gm. of standard digitalis powder, which is also kept at the same institution on behalf of the Health Organisation of the League of Nations.

The Mortality Curve

The principal difficulty with all biological assaying lies in the varying resistance of individual animals to the same dose of drug. This source of error has been largely overcome by applying the method worked out by J. W. Trevan. For digitalis he found that if the dose of a standard preparation was so regulated that it killed 50 per cent. of the frogs used in the test, then half that dose would kill only 5 per cent., and a dose one and a half times as much would kill all the animals. From his results he constructed a "mortality curve" characteristic for the influence of digitalis on frogs. This curve is shown in Fig. 1.

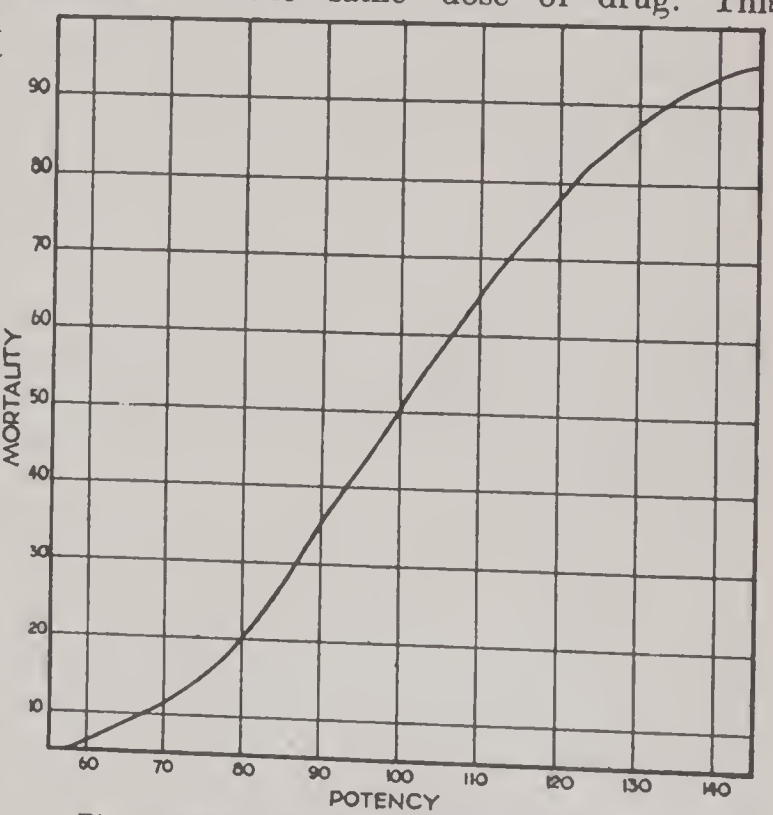


Fig. 1.—MORTALITY CURVE CHARACTERISTIC OF THE ACTION OF DIGITALIS ON FROGS

The Frog Test

An alcoholic extract of the standardised leaf is made under specified conditions and then diluted with water so that 10 ml. contains the active constituents of 1 gm. of the original powder. This extract is then suitably diluted with 0·6 per cent. aqueous sodium chloride solution. The same procedure is applied to the sample of digitalis leaf to be tested. At least 24 frogs of known weight are divided into two equal groups, and each frog of one group is given a dose of the standard extract, which is injected into the ventral lymph sac, the amount which each frog receives being directly proportional to its weight. The same procedure is followed with the other group of animals, using the extract of the sample under test. After 12 hours the number of deaths in each group is noted. As an example, let it be assumed that the result of an experiment was as follows :—

Sample	*Dose of Prepared Extract*	*Mortality*	*Percentage Mortality*
Standard	0·5 ml. per 100 gm. body weight	5 out of 12	42
Sample under test ..	0·5 ml. per 100 gm. body weight	8 out of 12	67

Referring to the curve, it is seen that 42 per cent. mortality corresponds to a potency of about 94 per cent. of the true standard, and that 67 per cent. mortality corresponds to 112 per cent. Hence it follows from this experiment that the strength of the sample under test is

$$\frac{100 \times 112}{94} = 119 \text{ per cent.}$$

of the standard preparation. The whole experiment is now repeated using a further 24 frogs. The dose of the standard is increased to 0·6 ml. per 100 gm. body weight in the expectation that this will produce 50 per cent. mortality, and the dose of the sample is likewise reduced to 0·4 ml. The result may be :—

Sample	*Dose of Prepared Extract*	*Mortality*	*Percentage Mortality*
Standard	0·6 ml. per 100 gm. body weight	7 out of 12	58
Sample under test ..	0·4 ml. per 100 gm. body weight	4 out of 12	33

From the curve it is seen that 58 per cent. mortality corresponds to a potency of about 106 per cent. of the true standard and that 33 per cent.

mortality corresponds to 89 per cent. Therefore, allowing for the different dosage, the strength of the sample under test is

$$\frac{100 \times 89 \times \cdot 6}{106 \times \cdot 4} = 126 \text{ per cent.}$$

of the standard preparation, the mean of the two experiments being 123 per cent. of the standard.

Biological Assay by the Cat or Guinea Pig Method

An alternative method of biological assay consists in slowly injecting a diluted extract of digitalis into the femoral vein of an anæsthetised cat, or guinea pig, in which the respiration is being artificially maintained. The injection of the drug is continued until the heart is arrested in systolic contracture, and the quantity of extract per kilogram body weight required to effect this is directly compared with the amount of standard material required to accomplish the same result. If the carotid artery be connected to a manometer charged with saturated sodium sulphate solution, the blood pressure may be observed during the injection of the digitalis extract and the moment of systolic arrest will readily be perceived by the sudden fall of the pressure to zero.

In using this method it is necessary to use 6 animals for each sample of digitalis tested and take the average reading. The quantity of standard extract required to arrest the heart must be determined by taking the average reading of 14 separate experiments, but, once the value is found, it is only necessary to check the figure at occasional intervals.

Powdered digitalis which is stronger than the standard is diluted, either by mixing with leaf which is below standard strength, or else with dried marc remaining after the preparation of tincture of digitalis. Those readers not hitherto aware of the need for biological standardisation of drugs may well be astonished to read this brief account of the elaborate and costly methods which it is necessary for manufacturers of medicines to adopt in order to ensure the uniformity and quality of their products.

CONVALLARIA FLOWERS

The dried inflorescence of lily of the valley is occasionally used as a substitute for digitalis for the treatment of cardiac disorders. The flowers, and also the rhizome of the plant, contain two glucosides termed convallamarin and convallarin, both of which have been obtained in crystalline condition. The drug is best administered as a 1 in 8 tincture made with 60 per cent. alcohol.

APOCYNUM

This is another drug which has been used as a substitute for digitalis. It consists of the rhizome and roots of certain species of *Apocynum*, herbaceous plants growing in the United States and Canada whence it has acquired the synonym "Canadian hemp." The active principle is a lactone called cynotoxin. The drug possesses a more powerful action on the heart than digitalis, but it is more irritating to the alimentary tract. Tincture of apocynum has been quite extensively used, particularly in America, as a combined tonic and diuretic for the treatment of cardiac dropsy.

STROPHANTHUS

The official drug consists of the ripe seeds obtained from *Strophanthus kombé*, a climbing plant of considerable size, indigenous to eastern tropical Africa, near the Nyanza and Tanganyika lakes. The seeds are about 15 millimetres long and 4 millimetres broad. An extract prepared from them is used in Africa as an arrow poison. The active constituent of the seeds is the glucoside strophanthin, of which they contain about 10 per cent. It is generally considered that strophanthin is a mixture of several different glucosides which have not been satisfactorily separated. Strophanthin occurs as colourless crystals with an intensely bitter taste, and it is readily soluble in water. When boiled with dilute mineral acid it is hydrolysed, forming strophanthidin and a sugar; the former, being almost insoluble in water, separates out as a crystalline precipitate.

Fig. 2.—STROPHANTHUS

The illustration shows the seeds and also two examples of the whole fruit, the larger of which is about 25 cm. long.

Chemical Test for Strophanthus Seeds

If the seeds are cut in half in a longitudinal direction and

the exposed surface moistened with a little sulphuric acid (80 per cent. by volume) the endosperm is coloured green. This colour is also given by two other species of strophanthus known as *S. hispidus* and *S. preussii*, but seeds from *S. courmontii* and *S. gratus* show a red coloration when subjected to this test.

Pharmacy of Strophanthus

This drug acts similarly to digitalis, but is more powerful ; in serious cases of cardiac weakness it is sometimes to be preferred to digitalis because it acts more quickly. On the other hand it is more toxic and greater caution in its administration is necessary. As in the case of digitalis, a tincture of the whole drug is more satisfactory than the purified active principle strophanthin. It is almost invariably employed in the form of tincture of strophanthus.

In preparing the tincture it is first necessary to extract the fatty oil from the seeds by maceration and percolation with light petroleum. The fat-free powder must then be removed from the percolator and dried ; the tincture is finally prepared by the percolation process, using 70 per cent. alcohol. Tincture of strophanthus is unique among the official tinctures in that the maximum recommended dose is only 5 minims whereas at least 15 minims is allowed for all other preparations of this class.

Standardisation of Strophanthus

A chemical determination of the total strophanthin does not yield results in accordance with the therapeutic activity of the drug owing to strophanthin being in reality a variable mixture of glucosides. The tincture is therefore assayed biologically, the methods being almost identical with those used for the standardisation of digitalis.

SQUILL

Squill is the bulb of *Urginea Scilla*, a plant abundant in the countries bordering on the Mediterranean Sea. There are two varieties of this drug, namely, white and red, the colour referring to the outer membraneous skin of the bulbs. In this country the white squill is preferred and appears in commerce cut into very pale yellow strips varying from 0·5 to 5 centimetres long. Red squill contains similar physiologically active principles to white squill but, in addition, there are present constituents which are toxic for rats and it is therefore used to poison these vermin.

Indian squill, or urginea, consists of the bulbs of *Urginea indica*, which is indigenous to India, and it is frequently employed as a substitute for the bulb of *Urginea Scilla*. The bulbs are rounded, conical or pear-shaped, the dimensions being about those of an average-sized onion. They are collected

Fig. 3.—Squill

This bulb is about 18 cm. high. The drug is generally imported after having been cut up into small flakes.

soon after the plant has flowered, divested of their dry membraneous outer scales, cut into slices and dried. The active principles appear to be similar to those of ordinary squill and the same formulæ and procedures are adopted for making the galenical preparations.

Chemistry of Squill

Little is known of the physiologically active constituents beyond the fact that they are glucosides; they have been separated into scillarin A and scillarin B, while a crystalline inactive substance called scillin has also been isolated. Minute, needle-like crystals of calcium oxalate are abundant and induce irritation if the crude drug is incautiously handled.

Pharmacy of Squill

Squill resembles digitalis in its action, but its effect on the heart is much more powerful. It is most generally employed in medicine as an expectorant, particularly in bronchitis, where the heart is often dilated following upon excessive coughing; in these cases squill corrects the heart trouble by reason of its cardiac action and at the same time increases the bronchial secretion and thereby assists towards an easier expectoration of sputum.

The active constituents of squill are readily extracted by macerating the bruised drug with diluted acetic acid. The preparation made on this principle is called vinegar of squill and is a 1 in 10 extract. Acetic acid is itself an expectorant and therefore assists the action of the vegetable drug. Syrup of squill is made by dissolving sugar in the vinegar and diluting with water to make a preparation approximately equivalent to 4·5 per cent of squill. Oxymel of squill is prepared by macerating bruised squill with acetic acid and water and after 7 days straining off and pressing the marc. The resulting liquid is heated to boiling and filtered while hot; to every 3 volumes of the cooled filtrate 7 volumes of honey is added, making a preparation containing approximately 5 per cent. of squill. These galenicals, together with a tincture made by the maceration process, are common ingredients of expectorant medicines.

There is no chemical method of standardising squill, but its cardiac

effect may be measured by the methods already described for digitalis. As, however, it is mainly used as an expectorant it is not usually necessary to apply any assay.

This concludes our brief survey of a group of vegetable drugs of profound importance. No artificial substitutes for them have been discovered ; they have incontestably proved their value in the alleviation of suffering and will continue to be a priceless boon to the human race.

Chapter IX

THE SAPONIN GLUCOSIDES

THESE glucosides form a soap-like froth when shaken with water. Even a very dilute aqueous solution of a saponin will produce a persistent froth when agitated. They are powerful protoplasmic poisons and many are strongly sternutatory. On hydrolysis the saponins yield various sugars, together with non-toxic compounds termed sapogenins. Four drugs containing saponins will be briefly considered, namely, quillaia, senega, sarsaparilla and hemidesmus. The first two are employed as expectorants, while sarsaparilla and hemidesmus are administered as alteratives in skin diseases.

Fig. 1.—QUILLAIA BARK
This is the chief source of commercial saponin.

QUILLAIA

This drug, also known as Soap Bark and Panama Wood, consists of the bark obtained from *Quillaja saponaria*, a large tree indigenous to Chili and Peru. It occurs in commerce in yellow or reddish flat pieces about a metre in length and 10 or 15 cm. broad. In fine powder quillaia is extremely irritating to the nasal membranes and induces violent sneezing.

Chemistry of Quillaia

The physiologically active constituents are two saponin glucosides—quillajic acid and quillaja-sapotoxin ; these two substances together form the " saponin " of commerce, and a good quillaia should yield about 10 per cent. of the mixture. The saponin content of quillaia bark may be determined in the following manner :—

Twenty gm. of the finely cut bark is extracted by boiling with four successive quantities of about 100 ml. of water, each extract being filtered off in turn. To the combined filtrates 50 ml. of concentrated hydrochloric acid is added and the mixture boiled under a refluxing condenser for an hour. This hydrolyses the saponins, forming sugars which are soluble and sapogenins which are insoluble. After cooling, the insoluble sapogenins are collected by filtering through two filter papers which have been previously counterpoised on a balance and folded together. The precipitate is washed with water until free from acid, dried at 100° C., and the amount of sapogenin determined by noting the difference in weight between the empty filter paper and the one containing the dried precipitate. One part of sapogenin is equal to 3·22 parts of saponin.

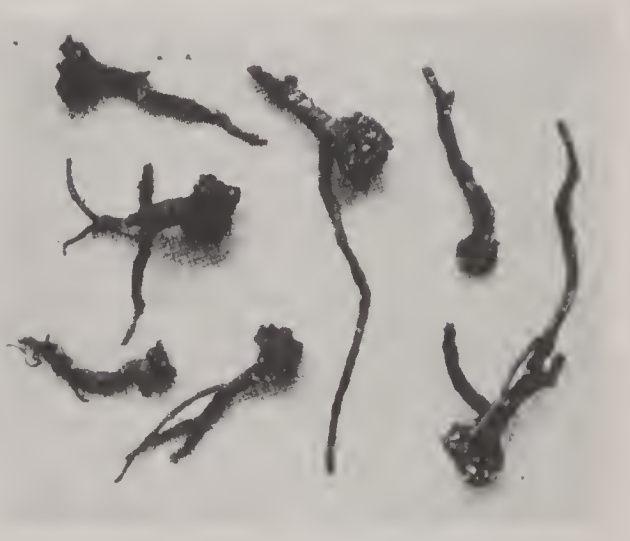


Fig. 2.—SENEGA ROOT

This root has been trimmed and dried. The larger pieces are 10 or 12 cm. long.

Pharmacy of Quillaia

Quillaia is generally used in the form of a tincture made by the percolation process with 45 per cent. alcohol. This preparation sometimes finds application as an emulsifying agent. A 1 in 1 liquid extract is employed as a wash for the scalp in certain skin diseases.

SENEGA

This is the root of *Polygala Senega*, a small perennial plant widely distributed over the United States. It occurs as slender brownish-yellow roots surmounted by a knotty crown to which the remains of purple scaly leaves adhere. The pieces are frequently much branched and may be about 8 cm. long.

Chemistry of Senega

The physiologically active constituents are the two saponin glucosides, senegin and polygalic acid. The drug also contains a small amount of methyl salicylate, which is responsible for imparting to the root the odour

of oil of wintergreen. No satisfactory method of standardising this drug has yet been devised, although there is reason to suppose that the commercial material varies considerably in its therapeutic activity. An interesting method of approximately measuring the activity has been proposed which depends upon the property possessed by saponins of hæmolysing defibrinated blood.

The Hæmolytic Test for Senega

The dried residue from 1 ml. of liquid extract of senega is dissolved in sufficient physiological saline solution to form a 0·5 per cent. solution. Physiological saline solution is a 0·9 per cent. aqueous solution of sodium chloride. In each of a series of test tubes 1 ml. of a 2 per cent. dilution of defibrinated blood, made with the same saline solution, is introduced, and then quantities of the senega extract solution from 0·1 to 1·0 ml. in increments of 0·05 ml., the volume of liquid in each tube being finally made up to 2 ml. with more saline solution. The contents of the tubes are mixed and allowed to stand 15 hours. The tube with the lowest senega content which shows complete hæmolysis is taken as the basis of calculation. Hæmolysis is indicated by the blood solution becoming transparent. The next lower tube should show a cloudiness on shaking. It has been found that different consignments of senega root vary considerably in their power of hæmolysing blood under these conditions.

Defibrinated blood is made by briskly stirring fresh blood with a bunch of twigs, when the fibrin, which is formed spontaneously when blood is drawn, is generated very rapidly and deposits on the twigs, leaving behind a red opaque fluid which will not clot.

Pharmacy of Senega

Little need be said in regard to the pharmacy of this drug. The most usual preparations are the fresh and concentrated infusions, the liquid extract and the tincture, all of which are prepared by the standard methods already described. Infusion of senega is usually administered with other expectorant medicines such as ammonium carbonate or preparations of ipecacuanha or squill.

SARSAPARILLA

Sarsaparilla is the root obtained from *Smilax ornata*, a climbing plant found in Central America. Several varieties of this drug are imported, that which is illustrated and known as "Jamaica" being the most common. The name does not indicate the country of origin, but arises from the fact that it was formerly exported via that country. Jamaica sarsaparilla occurs in bundles about 50 cm. long and 12 cm. in diameter.

It consists of numerous long reddish-brown slender roots, doubled up and bound loosely with one of the same roots. Other varieties include Honduras sarsaparilla, which is imported from British Honduras, Lima sarsaparilla, from Panama, and Vera Cruz or Mexican sarsaparilla, all of which are packed in characteristic ways.

Fig. 3.—SARSAPARILLA ROOT

This picture shows the way in which the drug is packed in bundles.

Chemistry of Sarsaparilla

Three saponin glucosides have been isolated and named parillin, smilasaponin and sarsasaponin. Smilasaponin is amorphous, while the other two have been obtained in crystalline form. The chemistry of this drug has not been extensively studied and little can be said of the constituents beyond mentioning their names. No satisfactory chemical methods for evaluating the drug have been devised, and, indeed, this can hardly be required unless its value as a medicine should become more firmly established.

Pharmacy of Sarsaparilla

The preparations in use include a liquid extract and a decoction made by the ordinary methods, and also a concentrated compound solution of sarsaparilla. This is made by infusing the bruised sarsaparilla with water for one hour at 71° C. After straining off the liquid the drug is infused twice more in the same manner and the infusions mixed. A decoction of a mixture of sassafras root, guaiacum wood, liquorice root and mezereon bark is then prepared, added to the mixed infusions and the resulting liquid evaporated, alcohol being added to prevent fermentation. After standing for a fortnight the preparation is filtered ; the final product should represent a 1 in 1 solution of sarsaparilla. This galenical is a useful vehicle for the administration of potassium iodide and is a usual constituent of the so-called " blood purifying " mixtures.

HEMIDESMUS ROOT

This drug originates from *Hemidesmus indicus*, a twining shrub growing throughout India and it is employed there as a substitute for sarsaparilla. The chemical characteristics have not been studied and the drug is only rarely used in European countries in the form of a syrup for flavouring purposes.

Chapter X

THE EMODIN PURGATIVES

THE chemical nature of the emodins has already been indicated in Chapter I. It is not yet certain whether the emodins of cascara, rhubarb and senna exist as glucosides but, in the case of aloes, there is no doubt as to the glucosidal nature of the emodin constituents.

CASCARA SAGRADA

This consists of the dried bark of the shrub *Rhamnus Purshiana*, which grows in North California, Oregon and Washington. Although the drug contains those derivatives of anthraquinone known as the emodins, it is doubtful if the laxative properties are entirely due to them, consequently, chemical standardisation does not satisfactorily determine its quality. Most of the available methods depend upon the fact that the dihydroxymethyl-anthraquinones form a deep, yellowish-red colour when dissolved in dilute aqueous solutions of the strong alkalis, such as ammonia or potassium hydroxide. The following method of evaluation is useful for comparative purposes.

Fig. 1.—CASCARA BARK

Fig. 2.—REFLUXING CONDENSER ATTACHED TO A FLASK IN ORDER TO PREVENT LOSS OF SOLVENT ON CONTINUOUS BOILING

The Determination of Emodins in Cascara

One gm. of the powdered drug is boiled for 2 hours with 25 ml. of dilute sulphuric acid and 100 ml. of chloroform, in a flask fitted with a refluxing condenser, which prevents any of the liquids evaporating. After cooling, the mixture is transferred to a separating funnel and the heavier chloroform in which the emodins have dissolved is drawn off from the aqueous part. More chloroform is added to the aqueous liquid remaining in the funnel and the mixture shaken. After allowing to separate once more the chloroform is again drawn off and added to the first portion.

Fig. 3.—SEPARATING FUNNELS IN USE FOR THE DETERMINATION OF EMODINS IN PURGATIVE DRUGS

In this way, all the emodins are transferred from the drug into a chloroformic solution, which is now reduced by evaporation to a volume of about 10 ml. This solution is transferred to a separating funnel and extracted in its turn with a 5 per cent. aqueous solution of potassium hydroxide by repeatedly shaking with convenient portions of the latter, allowing to separate and drawing off the chloroform into another separating funnel; this is continued until fresh additions of alkali solution are not appreciably coloured yellowish-red.

All the alkali extractions, containing the emodin originally present in the drug, are now mixed together and diluted with more 5 per cent. potash to 1 litre. The colour of this liquid is compared with that of a solution produced by dissolving 0·01 gm. of a pure emodin in 5 per cent. potash solution and diluting to 1 litre. The colours may conveniently be matched by "Nesslerising" (Fig. 4) or they may be expressed in arbitrary units by using a Lovibond Tintometer (see Chapter V, Fig. 8).

In regard to the empirical tests for cascara sagrada, it may be noted that the total ash should not exceed 6 per cent., and the water-soluble extractive should be about 20 per cent.

Pharmacy of Cascara Sagrada

An important preparation is the elixir, which is a sweetened liquid

preparation flavoured with volatile oils. Cascara sagrada has an intensely bitter taste, which is mitigated by storing the bark for a year before use and treating with alkaline substances such as ammonia, lime or magnesia. The elixir of cascara sagrada at present official in the British Pharmacopœia is made by moistening a mixture of the powdered drug, powdered liquorice root and light magnesium oxide with boiling water. The mass is stirred, allowed to macerate for 24 hours and then transferred to a percolator and the mixture percolated with boiling water until completely exhausted. The percolate is then concentrated by evaporation and the flavouring, consisting of oil of coriander, oil of anise, rectified spirit, and saccharin is added. Finally a quantity of glycerin is mixed in and sufficient water to produce a 1 in 1 elixir, which after standing for not less than 12 hours is filtered. Preparations of this type are free from objectionable taste and are extensively employed as mild laxative medicines.

Fig. 4.—The process of "nesslerising"
Colour matching by the method of trial and error.

The liquid extract and the dry extract are made by the general methods already described in Chapter I; the latter is used in the preparation of laxative pills.

FRANGULA

This is the bark of the alder buckthorn, *Rhamnus Frangula*, a shrub common in England and distributed generally over Europe. The active constituents are chemically allied to those of cascara, but the taste of frangula is stated to be less disagreeable, although its laxative property is equal. Notwithstanding this, it is but little used, and it need not be further considered.

RHUBARB

Medicinal rhubarb is the rhizome derived from certain species of *Rheum*. It mostly originates from Central and Western China where

the plant grows at high elevations on the mountains separating Tibet from the Chinese territory. It occurs as hard woody lumps of varying size and shape and usually covered with a yellowish adherent powder.

Fig. 5.—Rhubarb root
The natural root has been cut into pieces of a convenient size.

In addition to the emodin constituents, rhubarb contains a series of tannin substances. These appear to exist as glucosides, one of which, glucogallin, yields gallic acid and the sugar dextrose, when hydrolysed with dilute mineral acid. Free gallic acid is also present. It is the astfringent effect of these substances which causes the drug to exercise a constipating effect after the initial manifestation of its purgative action.

Chemical Tests for Rhubarb

The approximate determination of the emodin constituents which is conducted in the same manner as already described for cascara is of little value. The ash should not be more than 15 per cent., and the soluble extractive matter in 45 per cent. alcohol should not be less than 35 per cent. There is another species of this drug known as rhapontic rhubarb which does not contain emodins, but in their place a crystalline glucoside called rhaponticin. This variety of the drug is inferior and it can be detected by reason of its vivid violet fluorescence when examined in filtered ultra-violet light. It is of interest to note that the rhubarb grown in Britain for its edible stems appears to consist of hybrids of the rhapontic variety and *Rheum palmatum*.

Pharmacy of Rhubarb

The compound tincture of rhubarb is prepared by percolating a mixture of powdered rhubarb and powdered cardamom and coriander with 60 per cent. alcohol. After adding glycerin the preparation is adjusted to a 1 in 10 tincture with more alcohol. Coriander is a carminative and it also allays any griping effect which might follow the administration of rhubarb alone.

The compound powder of rhubarb, known as Gregory's powder, is made by mixing powdered rhubarb with a mixture of heavy and light magnesium carbonate and powdered ginger. A mixture of heavy and light magnesium carbonate is used in order to produce a powder of

convenient bulk. This is an old and tried preparation, and combines the virtues of a vegetable purgative with those of an antacid.

Purgative preparations are extensively prescribed in the form of pills and a compound rhubarb pill is official in the Pharmacopœia. This contains 25 per cent. of powdered rhubarb and 20 per cent. of aloes together with myrrh, hard soap and a little oil of peppermint.

SENNA

The two species of senna which are in general use are known in commerce as Alexandrian and Tinnevelly. The former is cultivated in the Upper Nile region, and the latter in Southern India. Alexandrian senna is

Fig. 6.—SENNA LEAVES AND PODS

the more highly regarded and consists of the dried leaflets of *Cassia acutifolia*, while Tinnevelly senna is derived from *Cassia angustifolia*. The former are about 2·5 cm. in length, while those of the Indian species may be nearly twice as long. The pods or dried fruits of both kinds are also extensively employed in medicine and consist of very flat greenish-brown legumes about 5 cm. long and 2·5 cm. wide.

Chemical Tests for Senna

The emodin of senna is thought to be the same as that contained in aloes, and is sometimes referred to as aloe-emodin. The following qualitative test detects the presence of emodins in senna leaves :—

Half a gm. of powdered senna leaves is mixed with 10 ml. of a 10 per cent. solution of potassium hydroxide in alcohol, and the mixture heated to boiling for 2 minutes, then diluted with 10 ml. of water and the liquid filtered. The filtrate is acidified with dilute hydrochloric acid and transferred to a small separating funnel. About an equal volume of ether is added and the mixture shaken for a few seconds and then allowed to stand. The ether, which now contains the emodins, will form a separate layer above the aqueous liquid. The lower layer is drawn off and rejected ; about 5 ml. of dilute ammonia is added to the ether and the mixture again agitated for a few moments. On allowing the immiscible liquids to separate, the lower ammoniacal layer will be coloured red.

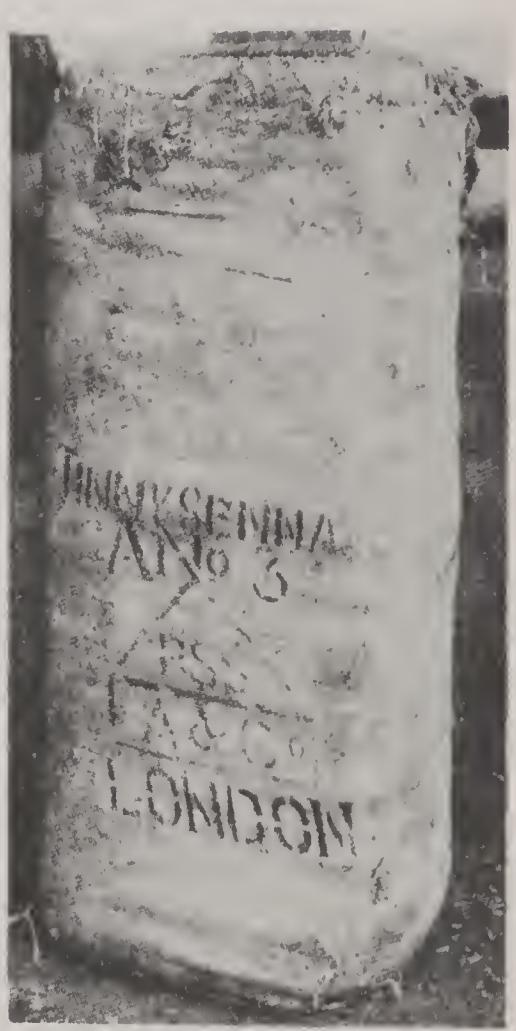


Fig. 7.—A BALE OF TINNEVELLY SENNA LEAVES
This bale weighs over 3 cwt.

Pharmacy of Senna

Senna is an efficient purgative either for occasional use or for habitual constipation. It is free from the astringent action of rhubarb, but, on account of its tendency to induce griping, is usually combined with carminatives and other laxatives. A few of the more important galenical preparations will be considered.

Confection of senna is the most important galenical in which senna leaves are employed, and is prepared by boiling gently for 4 hours in a covered vessel a mixture of figs, preserved tamarind fruit and prunes, with rather more than an equal weight of water. The softened pulp is rubbed through a sieve, the seeds and stones being rejected, and then mixed with cassia pulp, liquorice extract and cane sugar and, after warming, 100 gm. of powdered senna leaf and 40 gm. of powdered coriander fruit are mixed into the confection which is finally adjusted by the

addition of water, to weigh about a kilogramme. This preparation is pleasant to the taste and forms an excellent purgative in doses of about a teaspoonful.

Notwithstanding its name, compound liquorice powder owes most of its medicinal value to the powdered senna leaf which it contains. The official preparation of the Pharmacopœia consists of 16 per cent. each of senna and powdered liquorice root, together with powdered fennel, sublimed sulphur and 52 per cent. of sugar. It is an excellent laxative for use in habitual constipation.

The official liquid extract may be regarded as the basic preparation in which senna fruit is used. A weighed quantity of the crushed pods is macerated with five times as much chloroform water (2·5 volumes of chloroform dissolved in sufficient distilled water to produce 1000 volumes) for 8 hours, the liquid strained off and the maceration repeated a second and third time with a smaller proportion of chloroform water, the marc being finally pressed. The product of the macerations is then mixed with the strained liquid expressed from the marc and the whole evaporated under reduced pressure at a temperature not exceeding 60° C. until a 1 to 0·75 extract is produced. This is then diluted to a 1 to 1 extract by the addition of 90 per cent. alcohol. This galenical is considered to be the most active and reliable of the senna series and it forms the basis of the palatable syrup and elixir.

In order to prepare syrup of senna 1·5 parts of oil of coriander are added to 250 parts of the liquid extract and 300 parts of water added to the mixture, which is set aside for a day and then filtered. The filtrate is diluted somewhat with water, 700 parts of sucrose added and the product finally made up to 1000 parts with more water. Syrup of senna is an efficient purgative for the use of children and delicate persons.

The various elixirs constitute the most popular of all senna preparations and that included in the British Pharmaceutical Codex may be cited as typical of many in common use. Essentially, it consists of a mixture of equal proportions of liquid extract of senna and sucrose flavoured with oil of coriander and tincture of capsicum.

The fresh infusion is made by mixing senna fruit and sliced ginger with boiling water, allowing to stand for 15 minutes and then straining off the liquor. To make a concentrated infusion 800 gm. of senna fruit is percolated with 20 per cent. alcohol in the manner already described for preparing liquid extracts ; the first 700 ml. of percolate is reserved and percolation continued until about an additional litre of liquid has been collected ; this is evaporated until a pasty extract remains which is dissolved in the reserved percolate. After adding strong tincture of ginger, the volume is adjusted to 1 litre with 20 per cent. alcohol. These infusions are found to be particularly useful when mixed with the saline cathartics, such as Epsom or Glauber's salts.

The official compound mixture of senna is the well-known preparation

popularly called "black draught." It is made by mixing together liquid extract of liquorice, compound tincture of cardamom and aromatic spirit of ammonia and adding the mixture to a solution of magnesium sulphate (Epsom salt) in fresh infusion of senna.

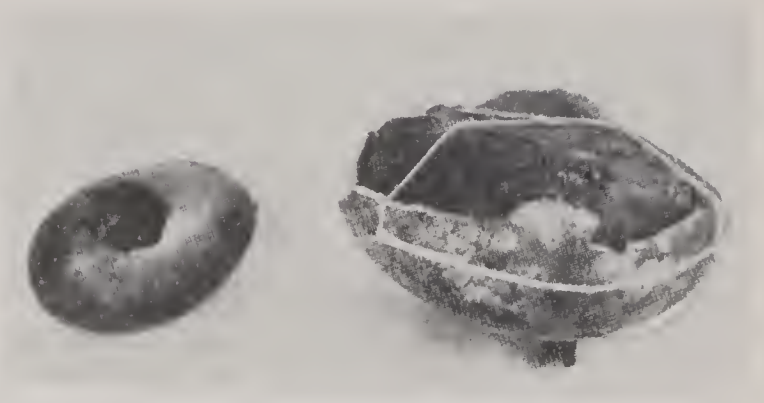


Fig. 8.—Aloes in gourds
The aloes, while liquid, is poured into the gourds and allowed to set.

ALOES

Aloes consists of the juice that flows from the transversely cut leaves of various species of *Aloe*, a plant belonging to the same natural order as the lilies. The character of the drug varies with the country of origin and the manner of drying the juice. The leaves, which are 30 to 60 cm. in length, are cut from the plant and placed, cut end downwards, in wooden troughs into which the juice drains. The juice is transferred to pans and boiled, and after reaching the desired consistency is poured into boxes or gourds and allowed to solidify.

Commercial Varieties of Aloes

Curaçao aloes was formerly produced on the island of Barbados and is often referred to as Barbados aloes, although it is now mostly produced on the East Indian islands of Curaçao, Aruba and Bonaire. It occurs as chocolate-brown or yellow opaque masses and breaks with a dull waxy fracture. Cape aloes which originates from Cape Colony is dark reddish-brown, and is transparent in thin fragments. It belongs, therefore, to the class of "glassy" aloes as distinguished from the opaque "livery" varieties.

Socotrine aloes is produced partly on the island of Socotra at the entrance to the Gulf of Aden and also on the East African mainland. It occurs as porous dark brown, opaque masses, while the variety of Socotrine aloes known as Zanzibar more nearly resembles Curaçao aloes, being yellowish-brown in colour and possessing a waxy lustre. Aloes has a bitter nauseous taste and a somewhat disagreeable odour.

Chemistry of Aloes

The principal constituent of aloes is the pale yellow crystalline glucoside aloin or barbaloin. Aloin is a derivative of tetrahydroxymethyl-anthraquinone and is, therefore, nearly related to the emodins. Curaçao aloes

contains between 10 and 30 per cent. of aloin, but the percentage of this glucoside in Cape and Socotrine aloes is not usually so high. Curaçao aloes contains another glucoside termed isobarbaloin, which is absent from all other varieties. The presence of isobarbaloin may be demonstrated by the following test, known as the " cupraloin " reaction, which therefore serves to distinguish Curaçao aloes from all other kinds.

The " Cupraloin " Reaction

Ten ml. of a 0·1 per cent. aqueous solution of the drug is mixed with 1 ml. of a 5 per cent. aqueous solution of copper sulphate ; about 1 ml. of a saturated solution of sodium chloride is added to this mixture followed by a few drops of hydrocyanic acid solution. The presence of isobarbaloin is indicated by the formation of a fine, deep claret coloration.

Tests for Purity

Attempts to work out methods for the chemical standardisation of aloes have not been very successful. The Cape variety may be distinguished from the others by mixing 5 ml. of a 0·1 per cent. aqueous solution with 2 ml. of concentrated nitric acid, when a yellowish-brown colour is produced which changes to a vivid green ; the other kinds do not yield a green colour under these conditions. The Pharmacopœia imposes an ash limit of 5 per cent., and states that the moisture determined by observing the loss in weight on drying at 100° C. should not exceed 10 per cent.

Pharmacy of Aloes

Aloes, which is an efficient purgative, is now almost always administered in pill form. The official pill contains about 58 per cent. of aloes together with hard soap, glucose syrup and a little oil of caraway. More generally, aloes is used in conjunction with other drugs such as carminatives or tonics. The Pharmacopœia includes a pill containing 30 per cent. each of aloes and asafetida, a gum-resin possessing valuable properties for the relief of flatulence. Salts of iron and extract of nux vomica are also mixed with aloes in pill form, and are used as general tonics, while preparations of belladonna are frequently added to minimise the griping effect of the purgative. Indeed, aloes is one of the most common of domestic medicines and is the basis of most proprietary " patent " pills.

COLOCYNTH

Although not containing emodins this drug may conveniently be mentioned here since it is an important purgative which owes its action to a glucosidal principle. Colocynth, or bitter apple, is the fruit of

Citrullus Colocynthis, a plant widely distributed throughout Northern Africa and Syria. It is cultivated in Syria, Spain and Cyprus and the north-western provinces of India. The fruit is about the size of an apple and, when ripe, is collected and peeled. Commercial colocynth fruits as imported form more or less broken white balls about 5 cm. in diameter. The light, whitish, pith-like pulp should be almost freed from the seeds, and it is stipulated in the Pharmacopœia that not more than 5 per cent. of the seeds originally present should remain. The fresh fruit usually contains between two and three hundred seeds.

Chemistry of Colocynth

The physiologically active principle is a pale yellow, intensely bitter, crystalline glucoside termed colocynthin. Other principles have also been isolated and named, but they are without therapeutic value. The Pharmacopœia imposes a limit on the amount of fixed oil present and states that not more than 3 per cent. of the drug shall be extracted by light petroleum. The acid-insoluble ash should not exceed 8 per cent.

Pharmacy of Colocynth

Colocynth is a drastic purgative and is therapeutically very much more powerful than any of the emodin group of drugs. It is rarely employed alone, being generally administered as an ingredient in various forms of laxative pills. The official pill of colocynth and hyoscyamus contains about 12·5 per cent. of powdered colocynth together with aloes, scammony resin, curd soap, oil of cloves and 12·5 per cent. of extract of hyoscyamus. The latter prevents the griping which would be induced by the administration of the purgatives alone.

The compound extract of colocynth is made by macerating crushed colocynth with 60 per cent. alcohol for 4 days, then straining and pressing the marc. The liquid thus obtained is evaporated to dryness, powdered and mixed with aloes, scammony resin, soap and cardamom.

It will be of interest to many readers to learn that colocynth is an ingredient of the Army pill No. 9. This famous medicament is a complex mixture of purgatives which includes calomel, rhubarb, aloes and scammony. The last-named belongs to a group of resinous drugs which are described in the next chapter.

Chapter XI

RESINOUS DRUGS

THE physiologically active constituents of the drugs described in this chapter are referable to the class of bodies termed resins. It is not possible to give a precise definition of a resin, but it may be said that they occur as amorphous brittle solids which soften when heated, and finally melt to a clear, adhesive fluid; a few resins are semi-solids at ordinary temperatures. They are all free from nitrogen but contain a large percentage of carbon combined with relatively small proportions of oxygen and hydrogen. When incinerated they burn with a smoky flame. Resins are insoluble in water but dissolve in alcohol, while some are soluble in ether. Under natural conditions certain resins are associated with gums and the mixed product is then termed a gum-resin. There are other resins which occur mixed with volatile oils or oily liquids and some of these substances are employed medicinally and form a class of drugs called oleo-resins.

Fig. 1.—SYRIAN SCAMMONY ROOT
This is usually packed in bales weighing 3 cwt. The size of each piece varies considerably, the specimens illustrated being about 10 cm. long.

SCAMMONY ROOT

This is obtained from *Convolvulus Scammonia*, a plant resembling the common bindweed but much larger, which is indigenous to the eastern Mediterranean countries. The roots vary from 1 to 10 cm. in diameter and may be up to about a metre long. The thicker end frequently retains the remains of aerial stems.

The roots are greyish-brown and often spirally twisted.

Chemistry of Scammony Root

The physiologically active principle is a resin, the amount present varying from 3 to 13 per cent. The resin is isolated by exhausting the powdered root by maceration and percolation with alcohol ; the resulting tincture is concentrated by distillation and the strong alcoholic solution slowly poured with constant stirring into about ten times its bulk of water. This operation precipitates the resin which is then collected on a filter, washed with boiling distilled water and finally dried.

Commercially, the resin is now obtained from ipomœa root, which yields a product which is considered to be identical with that derived from scammony root.

Commercial scammony resin occurs as brownish, translucent, brittle pieces, or as a brown powder. When highly purified it is nearly white and then consists almost entirely of scammonin, a glucosidal resin which on treatment with boiling dilute mineral acid yields scammonolic acid and the sugar dextrose.

Fig. 2.—Ipomœa root or mexican scammony root
This has been cut into transverse slices and the fibrous nature of the cut surfaces should be noted. This is the source of official Scammony Resin.

Scammony resin should contain at least 60 per cent. of ether-soluble matter and not more than 5 per cent. of moisture when dried at 100° C. When the ether-soluble portion of scammony resin is dissolved in a warm aqueous solution of potassium hydroxide it is not re-precipitated by the subsequent addition of an excess of mineral acid. This test serves to distinguish scammony resin from most other resins.

The Gum-Resin Scammony

Scammony, which should be clearly distinguished from either scammony root or scammony resin, is the name given to a gum-resin obtained by incision of the living root of *Convolvulus Scammonia* (scammony root). In collecting the gum-resin the roots are exposed by removing the surrounding earth and then cut slantwise, when the emulsion at once begins to exude and is collected in mussel shells inserted into the

roots at the lower end of the cut surface. The contents of the shells are collected, mixed into a homogeneous mass and allowed to dry. The best commercial qualities are known as virgin scammony and usually occur in large, flat, dark grey or blackish lumps possessing a characteristic odour and which are easily broken, thin fragments being yellowish-brown and translucent.

Good quality scammony contains about 80 per cent. of scammony resin, the remainder consisting mainly of gum. Owing to its high price scammony is liable to be adulterated by admixture with chalk or starch. The former is easily detected by determining the ash, which in genuine samples should not exceed 3 per cent., while the presence of starch may be revealed by a microscopical examination.

Pharmacy of Scammony Resin

This drug belongs to the group of resinous purgatives which includes jalap and podophyllum. They are generally administered in pill form ; very frequently two or more are combined in one pill, or they may be prescribed along with extract of belladonna or hyoscyamus, or with a small quantity of some carminative oil to prevent the griping which often accompanies their action. Galenical preparations of scammony root are not used as it is obviously more advantageous to start with the resin.

Compound scammony pill is made by mixing equal parts of scammony resin and jalap resin with powdered curd soap and tincture of ginger ; the mixture is evaporated to a suitable consistency and made into pills. Compound powder of scammony contains 50 per cent. of scammony resin together with powdered jalap root and ginger. In doses of 10 to 20 grains this acts as a powerful cathartic. Scammony resin finds a place in numerous recipes for laxative pills ; all these follow on the same lines, and contain an assortment of purgatives combined with carminatives like ginger and oil of peppermint, or with intestinal sedatives such as extract of hyoscyamus.

Pharmacy of Scammony

Owing to its high price and somewhat doubtful advantage over scammony resin the gum-resin is now but little used. The gum which is present in scammony causes it to emulsify readily with water or milk, and the British Pharmacopœia of 1885 included a preparation called scammony mixture. This was directed to be freshly made by triturating 6 grains of powdered scammony with 2 fluid ounces of milk until a uniform emulsion was obtained.

IPOMŒA

The root of *Ipomœa orizabensis* has now almost entirely replaced scammony root as a source of scammony resin. It is variously called

Mexican scammony root, Orizaba jalap root (from the town of Orizaba, about 60 miles from Vera Cruz), stalk jalap and male jalap. It should not be confused with jalap root obtained from *Ipomœa purga*, which contains a different resin.

Ipomœa is derived from a plant native to the Mexican Andes. The tuberous roots occur as cylindrical, fusiform grey or brown pieces 18 to 25 cm. long and about 10 cm. in diameter at their widest part. The root, as it occurs in commerce, is more usually cut into transverse slices or wedge-shaped pieces from about 1 to 4 cm. thick and 5 to 8 cm. wide. It is very hard and tough.

Ipomœa itself is not usually employed medicinally, but when extracted with 90 per cent. alcohol it yields from 10 to 20 per cent. of a resin which is said to be identical with that derived from scammony and is the product officially recognised by the British Pharmacopœia as scammony resin.

JALAP

Jalap consists of the dried tubercles of *Ipomœa purga*, a climbing plant indigenous to the Mexican Andes. The fresh tuberous roots which are fleshy and white internally are collected and dried in nets supported above fires; this treatment causes the drug to assume a deep, brown colour. Commercial jalap consists of irregularly oblong tubercles varying from 3 to 15 cm. in length, the larger pieces often showing longitudinal incisions which have been made to facilitate the drying process. The dark brown surface of the drug is wrinkled and marked with paler transverse scars known as lenticels.

The picture includes an example of an incised tubercle.

Chemistry of Jalap

The most important constituent is the resin of which there is usually from 8 to 12 per cent. The resinous material, isolated by exhausting the powdered root with strong alcohol and pouring the concentrated tincture into water, consists of two distinct resins one of which, constituting about

10 per cent. of the whole, is soluble in ether while the other is insoluble. The ether-soluble substance is considered to be identical with scammony resin while the remainder is called jalapin or convolvulin. When jalapin is treated with boiling dilute mineral acid it yields jalapinol (or convolvulinolic acid) and dextrose. It is, therefore, a glucosidal resin like that of scammony.

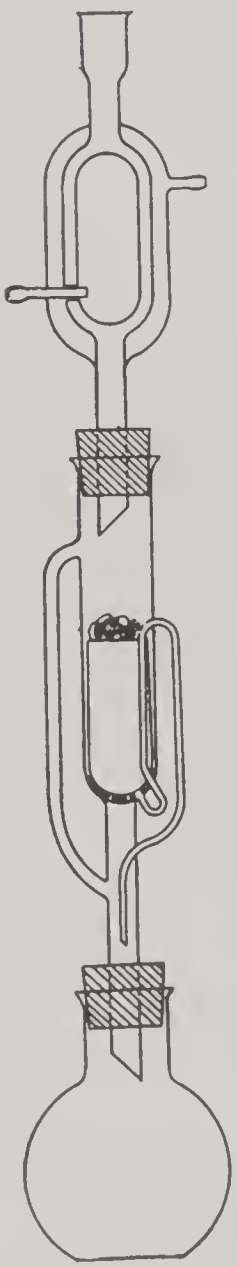


Fig. 4.—Soxhlet extractor

The material is introduced into a porous thimble of stiffened paper lightly plugged with cotton wool. The solvent is boiled in the flask and the vapour passes to the condenser via the wide side tube. The condensed liquid drops into the thimble and filters into the central chamber and the siphon tube. When the latter is filled, the central chamber is automatically emptied, the liquid being returned to the flask.

Assay of Jalap

The drug is evaluated by determining the percentage of total resin extracted by 90 per cent. alcohol. This solvent also dissolves other matter which is water-soluble and it is, therefore, necessary to treat the dried alcoholic extract with boiling water before weighing the resins. A weighed quantity of the powdered drug is introduced into an extraction thimble made of stiffened porous paper ; after the latter has been lightly plugged with cotton-wool it is inserted into a Soxhlet continuous extraction apparatus as shown in Fig. 4 and the drug is thoroughly exhausted with 90 per cent. alcohol, the solvent being circulated through the apparatus for some hours. The greater part of the alcohol is now removed by distillation or evaporation and the concentrated tincture transferred to a dish containing a stirring rod. The dish and stirring rod together should first be weighed. The remainder of the alcohol is now evaporated and the residue treated with boiling water in order to remove water-soluble extractive from the resins. The water is poured through a filter and the residue in the dish macerated with more boiling water which is again poured on the filter ; this operation is repeated until no more water-soluble matter remains. The resin on the filter paper is now dissolved by adding hot alcohol which is allowed to filter through into the weighed dish containing the bulk of the pure resins. This alcohol is now removed by evaporation and after drying at 100° C. the dish containing the resins and the stirring rod is weighed.

Pharmacy of Jalap

This drug is a very powerful purgative or hydragogue cathartic, and is employed in dropsy and Bright's disease to remove fluid from the body. The compound powder of jalap contains 30 per cent. of powdered jalap root mixed with powdered ginger and potassium hydrogen tartrate. Extract of jalap is made by macerating powdered jalap with about five times its weight of alcohol for 7 days, pressing out the solvent, filtering and removing the alcohol by distillation. The marc is macerated with water for several hours and, after straining through flannel, the aqueous extract is evaporated to a pasty consistency. This second extract is added to the first alcoholic extract and the mixture is evaporated by gentle heat until a firm residue remains. Extract of jalap is used for making pills. The alcohol-soluble portion of the extract contains the physiologically active resins, while the gummy and sugary matters of the aqueous extract help to subdivide the resins, in which state they are more active.

Jalapin is the ether-soluble portion of the resins from jalap and may be prepared by precipitating an alcoholic solution of the purified resin with ether. It occurs as a white, odourless powder. It is generally administered in pills made with syrup of glucose, soap and ginger or capsicum ; while it is also sometimes prescribed with calomel as a brisk purging medicine.

In order to avoid confusion it will be well to mention that in Germany the name " jalapin " is applied to the ether-soluble resin obtained from scammony root or from ipomœa.

KALADANA

The dried seeds of *Ipomœa hederacea* are used in India as a substitute for jalap. They are about 5 mm. in length, have a triangular-shaped transverse section, a small area around the micropyle being brown in colour while the rest of the coat exhibits an almost black matt surface. Minute cells in the cotyledons contain a resin called pharbitisin which is identical with jalapin, the ether-insoluble portion of jalap resin. Pharbitisin was included as an official drug in the British Pharmacopœia 1914 under the name Kaladana Resin. Kaladana is a powerful purgative which is usually administered as the compound powder containing 5 parts of the drug mixed with 9 parts of potassium hydrogen tartrate and 1 part of powdered ginger. It is sometimes employed in the form of a 1 in 5 tincture.

TURPETH

Turpeth consists of the dried root and stem of *Ipomœa Turpethum*, a native of India and Ceylon, and, like kaladana, is used in those countries as a substitute for jalap. The active constituent is about 10 per

cent. of a grey resin, insoluble in ether, called turpethin, which resembles jalapin. It may be observed that turpeth, kaladana, scammony root, ipomœa root and jalap all come from plants belonging to the Natural Order Convolvulaceæ, and that the physiologically active principles are all resins and all are purgatives.

PODOPHYLLUM

There are two species of podophyllum the rhizomes of which are used as vegetable drugs. *Podophyllum peltatum* or May-apple is a small herb which grows in the eastern United States and Canada. It occurs in commerce in reddish-brown approximately cylindrical pieces of variable

Fig. 5.—PODOPHYLLUM PELTATUM RHIZOME AND ROOT

This is the American podophyllum of commerce. It is usually exported in bales weighing 140 lb. each.

length and usually nearly 1 cm. in thickness. At intervals of about 5 cm. the rhizome is enlarged and bears on the upper surface a concave scar indicating the original seat of attachment of the aerial stems. The under side of the rhizome exhibits the scars of the roots when, as is generally the case, these have been detached. The drug has a slight characteristic odour and bitter acrid taste.

The other variety of this drug, known as Indian podophyllum, is derived from *Podophyllum emodi*, a plant which grows on the lower southern slopes of the Himalayas. The rhizome occurs in yellowish-

brown irregular, knotty pieces about 2 to 4 cm. long and 1 to 2 cm. thick. The upper surface is marked with cup-shaped stem scars, while the under surface may carry roots or, where these have been detached, their original position is marked by scars.

Chemistry of Podophyllum

When extracted with alcohol the American drug yields from 4 to 5 per cent. of resinous material, while 8 to 13 per cent. may be derived from the Indian variety. The resin obtained from the latter is thought to

Fig. 6.—PODOPHYLLUM EMODI RHIZOME AND ROOT

This is the Indian podophyllum of commerce. It is usually exported in bags weighing 28 lb. each.

possess about the same physiological activity as the American rhizome, but chemical reactions indicate that they are not identical. Besides the resin, podophyllum contains podophyllotoxin which is also extracted by alcohol. When isolated from the resin podophyllotoxin crystallises in colourless needles of definite melting point. It is soluble in many organic solvents, but only dissolves very sparingly in water. Medicinally its properties resemble those of the resin, since both are gastro-intestinal irritants.

Isolation of Podophyllum Resin

Podophyllum resin is more generally employed than galenicals made directly from the rhizome. It is prepared by exhausting the powdered drug with alcohol, recovering most of the alcohol by distillation, pouring the concentrated tincture into about ten times its volume of 1 per cent. aqueous solution of hydrochloric acid and allowing to stand for 24 hours. The precipitated resin is collected on a filter, washed free from acid with distilled water and dried at a temperature not exceeding 37° C. It occurs as a yellow or yellowish-brown amorphous powder insoluble in cold water but partially dissolved by hot water.

Tests Distinguishing the Two Kinds of Podophyllum

In the powdered state the two species of rhizome are not easily distinguished by their appearance, but they can be identified by chemical means. If 0·5 gm. of the powdered drug is macerated with about 10 ml. of 90 per cent. alcohol for a few minutes and the mixture filtered, the addition of a few drops of 5 per cent. aqueous solution of copper acetate produces a bright green colour with the American variety and a brown precipitate with Indian podophyllum. The difference in the chemical character of the resins accounts for these distinctive effects. If an alcoholic solution of the resin isolated from Indian podophyllum is rendered alkaline with potassium hydroxide solution the mixture at once forms a stiff jelly, whereas American podophyllum resin does not gelatinise under the same conditions. The resins may also be distinguished by determining the amount insoluble in 5 per cent. aqueous solution of ammonia, since that from *Podophyllum peltatum* contains only about 6 per cent., while approximately 45 per cent. of the resin from *Podophyllum emodi* remains undissolved.

Fig. 7.—DETERMINATION OF THE RESIN IN PODOPHYLLUM (1)

This shows the powdered root being extracted with boiling alcohol. The long tube attached to the flask acts as a refluxing condenser and prevents any loss of alcohol due to evaporation.

Evaluation of Podophyllum

The quality of the drug is judged by a determination of the total resin which may be conducted in the following manner :

A weighed quantity (10 gm.) of the drug is introduced into a flask containing 25 ml. of alcohol and the mixture is warmed at 80° C. on a sand-bath for 3 hours, the flask being provided with a cork carrying a piece of tubing to act as a refluxing condenser (Fig. 7). The mixture is then transferred to a small percolator fitted to a measuring cylinder (Fig. 8), and the drug is percolated with alcohol until 50 ml. of percolate has been collected. After mixing, 10 ml. of this tincture are transferred to a separating funnel, containing 10 ml. of chloroform and 10 ml. of 1 per cent. aqueous solution of hydrochloric acid. After the funnel has been shaken the immiscible liquids are allowed to separate and the lower layer is drawn off into another separating funnel. The liquid in the first separating funnel is extracted twice more, each time using about 15 ml. of a mixture of alcohol (1 vol.) and chloroform (2 vols.). The chloroformic extractions in the second separating funnel are now washed by shaking once with 1 per cent. solution of hydrochloric acid and after separating are drawn off into a tared flask. The upper acid layer is extracted twice more with small portions of the same chloroform-alcohol mixture and the latter run into the same flask. The solvent in the flask is then evaporated and the residue, consisting of the resin from 2 gm. of the original drug, is dried at 100° C. and the flask is again finally weighed.

Fig. 8.—Determination of the resin in podophyllum (2)

This is the next stage after the initial treatment with boiling alcohol. The drug is being percolated with additional alcohol until 50 ml. of percolate has been collected.

Determination of Podophyllotoxin

Podophyllum resin should contain at least 40 per cent. of podophyllotoxin. A method of determination has been suggested which depends upon the insolubility of podophyllotoxin in petroleum

ether. About 0·5 gm. of the powdered resin is accurately weighed into a small dry flask and 15 ml. of chloroform added. After allowing to macerate with frequent shaking for half an hour the chloroformic solution is filtered through a dry filter and 10 ml. of the filtrate at once added to 80 ml. of petroleum ether contained in a tared beaker. This throws the podophyllotoxin out of solution and, after allowing to stand a few minutes, as much of the precipitate as possible is collected in a tared Gooch crucible (Fig. 10) and the beaker and precipitate washed with 20 ml. of additional petroleum ether. The crucible and beaker are both dried at 70° C. for 1 hour and then weighed. The sum of their increase in weight is the amount of podophyllotoxin contained in two-thirds of the quantity of resin originally taken for the assay.

Pharmacy of Podophyllum

The resin of podophyllum is almost always employed in preference to extracts of the original rhizome. The drug is a drastic but slowly acting purgative ; it is usually administered in pills after being mixed with extract of hyoscyamus or belladonna and with other purgative drugs such as aloes or rhubarb. "Little Liver Pills" contain about three - twentieths of a

Fig. 9.—Determination of the resin in podophyllum (3)

Here the resin is being finally extracted with a chloroform-alcohol mixture.

Fig. 10.—Gooch crucible

The bottom is perforated with small holes and before use is evenly layered with finely divided asbestos by pouring an aqueous suspension of the latter into the crucible and attaching to a suction pump. Before weighing, the prepared crucible is dried by heating on a silica plate arranged above a Bunsen burner.

grain of podophyllum resin together with aloin, jalap resin, extract of hyoscyamus, dry extract of nux vomica and capsicum. A tincture of podophyllum consisting of a filtered solution of podophyllum resin in alcohol is occasionally used. This preparation forms a precipitate when mixed with water and a suggested improvement to overcome this trouble consists in making the tincture with aromatic spirit of ammonia in place of the alcohol.

GUAIACUM WOOD

This is a very hard, compact wood, heavier than water and dark greenish-brown in colour. It originates from *Guaiacum officinale* and

Fig. 11.—A GOOCH CRUCIBLE IN USE FOR THE DETERMINATION OF PODOPHYLLOTOXIN RESIN

The bottle on the right contains an aqueous suspension of fibrous asbestos for the preliminary preparation of the crucible. The left-hand bottle serves as a trap to prevent liquid entering the suction pump.

G. sanctum, evergreen trees, the former growing in the West Indies and the latter in many of the same islands and in southern Florida. It is imported in heavy logs and is mainly used in turnery, particularly for pulleys and other fittings for ships, while only the chippings and smaller blocks are found in the drug markets.

Chemistry of Guaiacum Wood

The physiologically important constituent is guaiacum resin which is present to the extent of 20 to 25 per cent. It is obtained from the wood

by raising one end of a log and firing it, when the heat melts the resin which flows out of a hole or groove cut in the other end. It occurs in commerce in rounded or ovoid tears or, more usually, in large blocks, and breaks easily with a clean glassy fracture, thin pieces being transparent and exhibiting a colour varying from yellowish-green to reddish-brown. The main constituent of the resin is guaiaconic acid which consists of a mixture of the amorphous α-guaiaconic acid, and the crystalline β-guaiaconic acid. Guaiaconic acid is colourless but it is readily converted by such oxidising agents as ferric chloride, ozone and hydrogen peroxide into a deep blue substance called guaiac blue.

Pharmacy of Guaiacum Resin

This drug, which is a mild laxative and diuretic, is employed in chronic rheumatism and gout. It sometimes relieves the pain and inflammation and if taken between the attacks may lessen the tendency to recurrence. The resin is also employed in the treatment of tonsillitis.

Guaiacum mixture, which is one of the more important galenicals, is made by mixing 2·5 parts of the powdered resin with an equal weight of powdered sucrose and 0·5 part of tragacanth and adding gradually with trituration sufficient cinnamon water to make 100 parts. Ammoniated tincture of guaiacum is a 1 in 5 preparation made by the maceration prócess using ammoniacal alcohol, the product being flavoured with oils of nutmeg and lemon. When this tincture is employed as an ingredient of a dispensed mixture the latter should contain mucilage of acacia in order to suspend the resin which precipitates.

Lozenges of guaiacum resin each containing 0·2 gm. are made by mixing 100 gm. of powdered drug with 6·5 gm. of tragacanth and 26 gm. of sucrose, both in fine powder, and adding sufficient of the black-currant paste of commerce to produce 650 gm. After rendering uniform by trituration, a little water being added if necessary, the mass is rolled out into a sheet of the correct uniform thickness and cut into 100 equal lozenges which are then dried at a moderate temperature. Guaiacum resin is employed in this form for the treatment of chronic tonsillitis and pharyngitis, especially when these conditions are associated with rheumatism.

Historical Note on Guaiacum Wood

This drug, which is often termed Lignum Vitæ, was first imported into Europe from the island of San Domingo in the early part of the sixteenth century and appears to have been held in good repute as a medicament, for it is recorded by Friedrich A. Flückiger and Daniel Hanbury in their "Pharmacographia" (1874) that treatises which appeared in Germany in the early part of the sixteenth century gave accounts of its use as a drug. One of these, dated 1519 and written by Ulrich von Hutton, was translated into English in 1533 by Thomas Paynel, canon of Merton

Abbey, and published in London under the title "Of the wood called Guaiacum that healeth the Frenche Pockes and also helpeth the goute in the feete, the stoone, the palsey, lepree, dropsy, fallynge euyll, and other dyseases." It was several times reprinted.

The "Frenche Pockes" refers to syphilis. At that time anyone laying claim to a knowledge of the healing art did all he could to find remedies for this disease. There is strong evidence for believing that syphilis originated in Europe with the return to Spain in 1493 of the expedition of Christopher Columbus following the discovery of the island of Haiti. The doughty adventurers who manned this enterprise contracted the disease from the natives of the West Indies and on landing in Europe promptly joined the army of Charles VIII of France on its invasion of Italy in 1494. Soon after this army had triumphantly established a court in Naples it became weakened through the ravages of a terrible venereal disease of unusual intensity, hitherto apparently unknown in Europe. In the following year the army retreated almost in a rout, the miscellaneous troops scattering all over the Continent to their respective home countries and carrying the new disease with them, while it was conveyed by the Portuguese to Africa and the Orient. The venereal nature and foreign origin of the complaint was well known and each nation tried to shift the responsibility to another, many peoples calling it the "French disease," others the "Spanish disease" and so on, while the Spanish alone seemed to be aware of its real origin in America and called it "española," which then meant Haiti. As is generally the case when a contagious or infectious disease is first introduced among a new people this scourge raged with unwonted severity and at the same time attacked all classes of society. Apart from the historical records, there is scientific evidence in support of the above account by reason of the absence of any bones showing signs of syphilitic attack in the numerous pre-Columbian relics in Europe and the abundance of such remains in America, many of which must certainly date prior to 1493.

Neither guaiacum wood nor any other vegetable drug was ever found to be of much avail against syphilis, and mankind struggled in vain with this dreadful scourge during four centuries. Then, in 1905, F. Schaudinn discovered the causative organism, *Treponema pallidum*, and in 1910 Paul Ehrlich and S. Hata introduced their famous organic arsenic compound "606" and brought relief at last.

INDIAN HEMP

We now turn to a resinous drug of quite a different kind from any of the foregoing. Indian hemp, also called Cannabis Indica, consists of the flowering tops of the pistillate plants of *Cannabis sativa* grown in India. Cannabis is an annual dicœcious herb, that is, the male and female flowers grow on separate plants, and it is cultivated in Europe for its strong fibres

known as hemp and also for its oily seed. When grown in tropical climates the pistillate flowers secrete a resin which possesses powerful narcotic properties ; this is not produced by the plant grown in temperate regions.

In India the pistillate plants are pruned in order to produce flowering branches which are then collected, allowed to wilt and pressed by treading them under the feet into compact flattened masses. The drug thus produced is exported from Bombay and is known on the London market as "guaza." In the districts to the north of Calcutta the gathered flowering tops are rolled under the feet of men who support themselves by grasping a horizontal bamboo pole and thus produce rounded masses of the drug. This variety is termed Bengal "ganjah" and is physiologically more active, but is not seen in commerce in England. The larger leaves and young twigs are also dried and form the drug called "bhang," which is mostly consumed in India. Another practice consists in beating the plants on cloths to which the resin adheres ; a greenish - brown soft mass is obtained which is freed from debris by warming and pressing through cloths. The product is termed "charas" or "churrus" and, like "ganjah," is smoked by Indian and Eastern races with the object of producing an agreeable form of intoxication.

Fig. 12.—INDIAN HEMP

In the drug trade this substance is usually called Cannabis Indica. Its sale and distribution is subject to the rigid restrictions of the Dangerous Drugs Acts.

In English commerce the drug usually occurs as flattened, compressed, rough masses of dull green colour which are resinous to the touch. The pieces, which vary in length from 5 to 30 cm., consist of a straight stem with ascending branches bearing numerous curved hairs and stalked glands, the latter secreting a viscid adhesive resin.

Chemistry of Indian Hemp

The resin is undoubtedly the part of the plant responsible for its narcotic action. This can be separated as a soft brown substance termed cannabinone, from which by distillation under reduced pressure a viscous resin has been separated. This melts to an oily liquid when warmed and

is called cannabinol ; it is believed to be the active constituent of the drug. On exposure to the air it rapidly becomes less active. The same deterioration occurs more slowly in the drug itself and good qualities should not be more than a year old. The total resin in Indian hemp amounts to 15 or 20 per cent.

In addition to cannabinone, the drug contains traces of the base choline and also a small amount of volatile oil. The ash (mineral matter) varies between 15 and 18 per cent., and the alcohol extractive is generally about 18 or 20 per cent. Although the material extracted by alcohol includes the resin the quantitative determination is of little use for the evaluation of the drug, since the cannabinol, originally present in the resin, may have oxidised with the consequent loss of its medicinal property.

Chemical Identification of Indian Hemp

Although it is not possible to apply a chemical assay to this drug, it is sometimes of importance to establish that powdered specimens belong to the medicinal variety of hemp. The following test is useful in this connection :—

About 0·1 gm. of the powdered sample is macerated for 3 minutes with 5 ml. of petroleum ether and the liquid filtered. To 1 ml. of the filtrate 2 ml. of a 15 per cent. solution of hydrogen chloride in absolute alcohol is added. If the reaction is positive a red coloration appears at the junction of the two immiscible liquids and, after shaking, the upper layer becomes colourless while the liquid underneath acquires an orange-pink colour which disappears on the addition of 1 ml. of water.

Pharmacy of Indian Hemp

Owing to its uncertain action and the absence of satisfactory means of standardisation, the medicinal application of Indian hemp is declining. It is no longer an official drug in this country, but is included in the United States Pharmacopœia. A soft extract made by percolating with 90 per cent. alcohol and evaporating the percolate was official in the British Pharmacopœia 1914. This is used for incorporation into pills after massing with diluents such as powdered liquorice root. A 5 per cent. solution of the soft extract in 90 per cent. alcohol constitutes the tincture of Indian hemp which is an ingredient of an important preparation known as compound tincture of chloroform and morphine ; it is also included in many of the recipes for " chlorodyne." Both these galenicals are used in the treatment of diarrhœa, colic and bronchial coughs, but as their action is principally due to the morphine which they contain, they have been described in the chapter dealing with opium.

Biological Assay of Indian Hemp

A proposed method of standardisation depends upon the power of Indian hemp to produce incoördination in the muscular action of dogs.

A standard liquid extract is prepared by the usual percolation process from a powdered mixture of not less than ten samples of the drug. The strength of this preparation is so adjusted that it will produce muscular incoördination when administered by the mouth to dogs in a dose of 0·03 ml. per kilogramme body weight. Before administration, the extract should be introduced into gelatin capsules. Liquid extracts prepared from individual consignments of the drug are so adjusted in strength that when given to dogs in the same dose they produce an equal physiological effect. The solid pilular extract is similarly standardised and is seven and a half times stronger than the liquid preparation. At the best the method can only give a very approximate estimate of potency, but it is better than any known qualitative chemical test.

Physiological Effect of Indian Hemp

This is a narcotic drug, acting chiefly on the central nervous system, and is occasionally used as an anodyne sedative in cases of sleeplessness due to nervous exhaustion or acute neuralgia. In this country the sale and use of Indian hemp and its preparations are now subjected to the rigorous restrictions imposed by the Dangerous Drugs Acts, and its use for any but medical purposes is unlawful. In Asiatic countries and in Africa it is used as an intoxicant, and it has been stated that upwards of one hundred millions of mankind habitually indulge in its questionable virtues. Some of the preparations are smoked, either alone or mixed with tobacco, others form intoxicating drinks or they may be compounded with sugar to produce confections.

Soon after its administration the devotee passes into a dreamy, semi-conscious state in which the normal judgment is lost and the imagination untrammelled by the irksome realities of life. The sense of time and space is confused and the dreamer may fancy himself transported to gardens of paradise amidst scenes of indescribable beauty ; or it may seem that he is being wafted over the hills and over the sea to the ambient purities of Elysium, where the fretful worries of life are gone for ever. Slowly the aureate vision recedes and gently leads the way to tranquil sleep.

Chapter XII

DIURETICS, EMMENAGOGUES AND APHRODISIACS

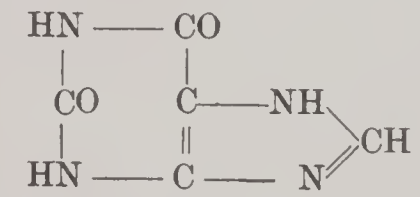
UNDER one or other of these headings vegetable drugs which are administered for their action on the various genito-urinary organs will be discussed. Only a few items are of any importance since, in general, the disorders affecting this part of the body are better treated by synthetic chemical drugs or by hormones of animal origin.

DIURETICS

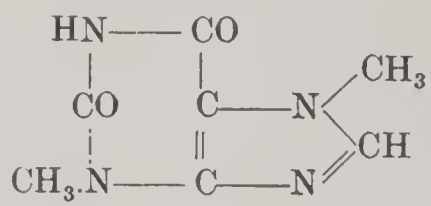
These are substances which increase the secretion of urine. The need for augmenting the normal flow arises in cases where there is a pathological accumulation of fluid in the body as, for instance, in cardiac, hepatic and renal dropsy.

CAFFEINE, THEOBROMINE AND THEOPHYLLINE

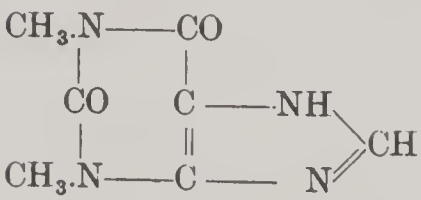
The most notable diuretics derived from vegetable sources are caffeine and theobromine, which are purine derivatives closely related to the xanthine bodies found in the urine and tissues of animals : theobromine is 3 : 7-dimethyl-xanthine and caffeine is the 1 : 3 : 7-trimethyl derivative :—



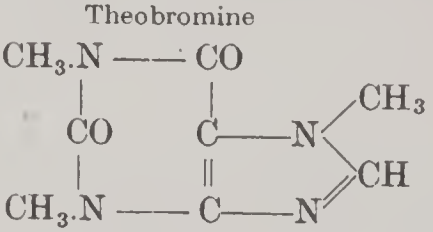
Xanthine



Theobromine



Theophylline



Caffeine

Theophylline, which is isomeric with theobromine, one of the methyl groups being attached to a different part of the molecule, only occurs in small amounts in vegetable products and is generally made synthetically. The important natural sources of these drugs are indicated in Table VI.

It will be seen that the amount of caffeine in tea is appreciable and this largely accounts for its popularity as a beverage since caffeine, besides being a diuretic, is a stimulant to the central nervous system. It

is generally considered that an average cup of tea or coffee contains approximately a grain of caffeine. Although the proportion of caffeine in coffee is only about half that present in tea this is compensated, since more of the former is used for making a beverage.

Determination of Caffeine in Tea

It is sometimes useful to know the caffeine content of tea samples, particularly of residues such as tea dust and sweepings which frequently serve as commercial sources of the drug. The following method is representative of the procedures usually employed :—

A suitable quantity of the sample, usually 10 gm., is introduced into a Soxhlet apparatus (see page 124) and extracted with 95 per cent.

TABLE VI—PRINCIPAL NATURAL SOURCES OF CAFFEINE AND THEOBROMINE

Plant	*Part of Plant Used*	*Countries of Origin*	*Approximate Content of Caffeine per cent.*	*Approximate Content of Theobromine per cent.*
Cacao or Cocoa ..	Seed ..	Tropical America, Java, Ceylon, W. Indies, etc.	—	2
Coffee	Seed ..	Jamaica, Ceylon, Mysore, Java, etc.	0·5 to 2	—
Guarana	Prepared Seed	Brazil and Uruguay ..	2·5 to 5	—
Kola or Cola ..	Seed ..	W. Africa and W. Indies, Brazil and Java	2 to 2·5	Trace.
Maté or Paraguay Tea	Leaf ..	Brazil and Argentine ..	0·2 to 2	—
Tea	Leaf ..	China, Japan, Assam and Ceylon.	1 to 5	Trace : and a trace of theophylline.

alcohol for about 8 hours. The alcoholic extract is added to 10 gm. of magnesium oxide suspended in 100 ml. of water and the mixture evaporated nearly to dryness on a water-bath. The resulting paste is wetted with alcohol, transferred to a filter and the caffeine washed out with about 250 ml. of hot water. To the filtrate, containing the caffeine, is added 20 ml. of dilute sulphuric acid, the mixture is gently boiled in a capacious flask for about an hour, allowed to cool and transferred to a separating funnel. The acid solution is now extracted six times with successive 20-ml. portions of chloroform, the mixed chloroformic extract is washed with 5 ml. of a 1 per cent. aqueous solution of sodium hydroxide

and the latter re-extracted with 10 ml. of chloroform. The combined chloroformic extracts are evaporated in a tared flask, the residue of caffeine dried at 100° C. and weighed.

The caffeine thus obtained is not quite pure and, in order to ascertain the true proportion, it is customary to determine the nitrogen content of the residue by the Kjeldahl process. Briefly, this consists in heating the residue with a little concentrated sulphuric acid and potassium sulphate until it is completely oxidised, allowing to cool, diluting with water, transferring to a distillation apparatus, adding an excess of sodium hydroxide solution, distilling, collecting the ammonia liberated into a known volume of standard acid and finally titrating the excess of the latter. The result of the titration is calculated to percentage of nitrogen present in the residue as originally extracted and the value obtained converted to pure caffeine by multiplying by 3·464. Generally the results obtained by direct weighing are about 0·05 per cent. higher than those calculated from the nitrogen figure.

Determination of Caffeine in Kola

This may be conducted more easily than in the case of tea and the following simple procedure serves well :—

A weighed quantity (7 gm.) of the powdered seed is transferred to a flask and 70 ml. of chloroform added. After standing for a few minutes 4 ml. of dilute ammonia is introduced, the flask shaken at intervals and, after 1 hour, 40 ml. of the mixture (equivalent to 4 gm. of the sample) is filtered through a plaited paper and the filtrate evaporated. The residue is treated with 2 ml. of chloroform and 15 ml. of hot water, the mixture very gently boiled for 5 minutes, the hot liquid filtered into a tared dish and the filter and residue in the flask washed with three 10-ml. portions of hot water, the washings being added to the main liquid in the tared dish. This purified aqueous extract is evaporated to dryness, the residue, consisting of caffeine and a trace of theobromine, is dried at 100° C. and weighed. Kola of good quality should yield not less than 1·5 per cent. of the two xanthine derivatives.

Properties of Caffeine and Theobromine

Caffeine occurs in the form of white, odourless, flexible, glistening silky needles, usually matted together and having a bitter taste. As found in commerce it generally contains about 7 per cent. of water of crystallisation but it becomes anhydrous at 100° C. In commerce these xanthine derivatives are frequently termed "alkaloids," but they are more correctly classified as purine bases. Their basic property is extremely feeble and, as will be seen from a study of the method given for the assay of tea, caffeine may be extracted from acid aqueous solutions by shaking with chloroform. Besides its use as a diuretic, caffeine is administered in tablet form in association with aspirin and phenacetin

in the treatment of nervous headache. Another useful combination of the same type is phenazone and caffeine, the stimulant action of the latter compensating the depressing effect of the former.

Caffeine forms loosely combined salts with acids, the most widely used being the citrate. This is more soluble than caffeine itself, 1 part dissolving in about 32 parts of cold water as compared with the 80 parts of water required by the free base. It is employed as effervescent caffeine citrate which comprises a mixture of sodium bicarbonate, tartaric acid, citric acid together with sugar and contains about 2 per cent. of caffeine base.

The double salt of caffeine and sodium benzoate which contains between 47 and 50 per cent. of the anhydrous purine base is readily soluble in water (1 in 2) and is used hypodermically as a cardiac and respiratory stimulant or as a diuretic. The analogous double salt of caffeine and sodium salicylate is even more soluble in water and its solutions are similarly employed for parenteral administration.

Theobromine has hardly any stimulant action on the central nervous system and, in consequence, is often preferred to caffeine as a diuretic drug, particularly as it has a more powerful action on the kidneys. The free base, which occurs as an odourless, white crystalline powder, is only slightly soluble in water (1 in 1700) and, moreover, does not readily dissolve in organic solvents. It is generally employed as the very soluble double salt, theobromine sodium salicylate, being administered in mixture form in the treatment of chronic Bright's disease and cardiac dropsy.

Theophylline has a more marked diuretic action even than theobromine but is liable to cause digestive disturbance : it is employed as the soluble theophylline sodium acetate.

The Murexide Test

If a few drops of concentrated hydrochloric acid are added to a trace of a purine contained in a dish and, after the addition of a crystal of potassium chlorate, the liquid is evaporated to dryness and the residue exposed to the vapours of ammonia, a fine purple colour is produced, due to the formation of murexide which is the ammonium salt of purpuric acid. This is a generic qualitative reaction given by all purines, including uric acid.

Assay of Theobromine Sodium Salicylate

This substance is best regarded as a mixture of sodium theobromine and sodium salicylate in approximately molecular proportions rather than as a true chemical compound. The British Pharmacopœia stipulates that the dried material shall contain not less than 46 per cent. of theobromine, not less than 41 per cent. of sodium salicylate and not more than 6·9 per cent. of sodium (calculated as Na) additional to that contained in the sodium salicylate. In order to determine the sodium

salicylate the bulk of the theobromine is first separated by precipitating it with dilute ammonia and filtering the mixture ; the filtrate is then acidified with dilute hydrochloric acid, the liberated salicylic acid extracted by shaking with ether, the ethereal solution washed, the solvent evaporated and the residue titrated with standard sodium hydroxide solution. The additional sodium, which is purposely added during manufacture in order to prevent the material becoming insoluble in water due to the absorption of carbon dioxide from the air, is determined by direct titration with standard acid using phenol red indicator.

The method used for the determination of theobromine, due to P. A. W. Self and W. R. Rankin, is of special interest and involves the quantitative conversion of the theobromine (dimethyl-xanthine) into caffeine (trimethyl-xanthine) by means of dimethyl sulphate. The caffeine so produced is then isolated by extraction with chloroform and the weight of dried material found is calculated to its equivalent of theobromine. This mode of procedure was suggested owing to the difficulty of extracting theobromine directly, it being only dissolved in slight degree by organic solvents. The determination is conducted in the following manner :—

About 1 gm. of the sample, accurately weighed, is dissolved in 10 ml. of water contained in a stoppered flask, 2 ml. of normal sodium hydroxide added followed by 0·6 ml. of dimethyl sulphate. The mixture is shaken for 5 minutes, set aside with occasional shaking for 30 minutes, then a further 3 ml. of normal sodium hydroxide added. The liquid is transferred to a separating funnel with the aid of a little water and the caffeine (methylated theobromine) extracted by shaking with successive portions of chloroform, each chloroformic extract being washed with water contained in another separating funnel. The solvent is removed by distillation, the residue dried at 100° C. and the proportion of theobromine in the sample derived from the yield of caffeine by applying the factor 0·9278.

BUCHU

Official buchu consists of the dried leaves of *Barosma betulina*, a small shrub indigenous to Cape Colony. The pale green leaves are 1 to 2 cm. in length. Their shape is characteristic, being officially described as " rhomboid-obovate," while the margins exhibit numerous small sharp teeth. These features are shown in Fig. 1. The leaves possess a strong and characteristic odour. Two other varieties of buchu are frequently imported, namely, *Barosma serratifolia* and *Barosma crenulata*, known respectively as " long " and " crenate " buchu by contrast with the official or " short " buchu. The leaves of " long " buchu are lanceolate and not more than 0·5 cm. in width and vary from 2 to 4 cm. in length while the " crenate " variety has leaves of similar length but somewhat broader.

Chemistry of Buchu

This drug yields from 1·3 to 2·5 per cent. of a dark coloured volatile oil, the most important constituent of which is a ketophenol called diosphenol which tends to crystallise from the oil. Diosphenol, which is also called buchu "camphor," is the substance responsible for the therapeutic value of the drug. The volatile oil derived from the "long" and "crenate" buchu only contains traces of diosphenol, hence these varieties should be avoided for pharmaceutical purposes. The oil contains about 30 per cent. of diosphenol, the remainder consisting largely of terpenes together with a ketone stated to be allied to menthone, which is one of the constituents of peppermint oil. Besides the oil, the drug contains mucilage, yellow crystals of hesperidin and a therapeutically unimportant glucosidal substance termed diosmin.

Fig. 1.—Buchu leaves

This drug is imported in bales weighing from 2 to 2½ cwt.

Evaluation of Buchu

Any assay method designed test the value of buchu aims at a determination of the diosphenol. Very little work has been done in this direction, but it will be interesting to describe briefly a procedure suggested by a Dutch investigator, M. de Waal.

Twenty gm. of the powdered leaves is introduced into a stoppered flask containing 300 ml. of water and the mixture allowed to macerate in a dark place for 24 hours. The liquid is then distilled until a drop of the fresh distillate no longer gives a green colour when tested with a drop of ferric chloride solution, thus indicating that all the diosphenol has been transferred to the distillate. The latter is now mixed with 1 ml. of 10 per cent. solution of ferric chloride and, after allowing the mixture to remain in the dark for 1 hour, the excess of ferric chloride over that consumed in oxidising the diosphenol is determined by adding 2 ml. of hydrochloric acid together with 2 gm. of potassium iodide and titrating the liberated iodine with decinormal sodium thiosulphate employing starch as the indicator. The difference between the reading thus obtained and the titre due to a control applied directly to 1 ml. of the

original ferric chloride solution gives the number of ml. of sodium thiosulphate corresponding to the diosphenol present in the 20 gm. of drug taken for the assay. From the results of several assays de Waal found that 20 gm. of powdered buchu gave an average value equivalent to 2·1 ml. of decinormal sodium thiosulphate.

Pharmacy of Buchu

This drug is used for the alleviation of inflammatory conditions of the urinary organs. The most important galenical is the fresh infusion which is a 1 in 20 preparation made by the standard method already described (see page 10). A more convenient galenical for dispensing purposes is the concentrated infusion prepared by percolating the freshly broken leaves with 25 per cent. alcohol, reserving the first portion of the percolate and continuing the percolation until the drug is exhausted. The second liquor is then evaporated to an extract of syrupy consistency which is dissolved in the reserved portion and the volume adjusted to make a preparation eight times stronger than the fresh infusion.

Compound buchu mixture consists of the fresh infusion with about one-thirtieth its volume of tincture of hyoscyamus and 20 grains of potassium citrate in each fluid ounce. This preparation is used as a diuretic and urinary sedative for the treatment of cystitis and similar disorders.

BEARBERRY
(UVÆ URSI)

Bearberry, *Arctostaphylos Uva-ursi*, is an evergreen shrub distributed throughout North America and Northern Europe. The leaves have long been used for medicinal purposes, but more efficient drugs are now tending to displace them. Bearberry leaves are about 2 cm. long by 1 cm. broad, the margins being entire. The upper surface is shiny and dark yellowish-green, while the under surface is slightly paler.

Fig. 2.—Bearberry leaves or uvæ ursi

These leaves have a somewhat leathery texture. The imported drug is packed in 100 lb. bags.

Fig. 3.—Broom

This is the only British species of *Cytisus*. It is an elegant shrub frequently seen in gardens: in the early part of the summer the wild plant bears yellow flowers.

Chemistry of Bearberry

Bearberry contains about 6 per cent. of tannin, together with gallic acid and quercetin. There is also present a glucoside termed arbutin, which crystallises in white needles. When arbutin is hydrolysed by treatment with dilute mineral acid, hydroquinone and dextrose are formed. This decomposition takes place when arbutin passes through the body, and the medicinal merits of bearberry are thought to be partly due to the antiseptic properties of the hydroquinone thus produced.

Pharmacy of Bearberry

Since the introduction of the much more efficient diuretic drugs of the caffeine series the value of bearberry has declined and it has been omitted from the present British Pharmacopœia. It is usually administered as the infusion made by adding to the bruised leaves twenty times their weight of boiling water, allowing to infuse for 15 minutes, and straining. Infusion of bearberry serves as a useful vehicle for other diuretic or antiseptic medicaments, especially in those cases where an astringent action is also desirable.

BROOM TOPS (SCOPARII CACUMINA)

The flowering tops of the broom (*Cytisus scoparius*), a leguminous shrub widely distributed throughout England and temperate Europe, are sometimes employed as a feeble diuretic in dropsical complaints of cardiac origin. The tops are used both fresh and dried. The drug

contains a yellow crystalline phenolic substance called scoparin, to which the diuretic action of broom is due and also the liquid, volatile alkaloid sparteine. Juice of broom, prepared by subjecting the bruised, fresh tops to pressure and adding to the expressed liquid one-third its volume of alcohol, was included in the British Pharmacopœia 1914. This, and the infusion, for which the dried drug is used, may be regarded as the most important galenicals.

Decoction of broom is made by adding 5 parts of dried tops to 100 parts of water, boiling for 10 minutes, straining and, if necessary, making up with more water to produce 100 parts of finished product. This preparation is sometimes dispensed with squill and ammonium acetate for the treatment of dropsical conditions.

COPAIBA

Copaiba is an oleo-resin, obtained by boring into the base of the trunks of various species of *Copaifera*, large trees indigenous to Brazil and the northern regions of the South American continent. It occurs as a yellow or golden-brown, viscous and generally transparent liquid with a characteristic aromatic odour, but the appearance differs to some extent according to certain recognised commercial varieties: thus Para copaiba is thin, transparent, and yellow, while Maranham and Maracaibo are both more viscid, darker in colour and translucent. The drug consists of varying proportions of resin and volatile oil, the Pharmacopœia specifying that the official material shall contain between 50 and 65 per cent. of the former as measured by the proportion of residue remaining after driving off the volatile oil by heating on a water-bath until a constant weight of resin is obtained.

Fig. 4.—Determination of the amount of resin in copaiba

The copaiba has been dried in a nickel dish, and, after cooling and weighing, the under-surface is tapped sharply with a lead pencil.

Copaiba is a product liable to be adulterated, and it is therefore necessary to submit consignments to careful analytical control. The drying test designed to determine the proportion of volatile oil and resin is usually conducted in a flat-bottomed nickel dish and as the volatile constituents are evolved the odour should be noted from time to time

in order to confirm the absence of turpentine. The dried resin from genuine copaiba is exceptionally brittle, a fact which may be noted by tapping the underside of the dish with a pencil (see Figs. 4 and 5). It is often advisable to isolate the volatile oil by distilling it from the oleo-resin under reduced pressure, or, as it is frequently termed, *in vacuo*. This is conducted by connecting a flask containing the oleo-resin to a condenser by means of a splash head and fitting a receiving flask with a side tubulure leading to a vacuum pump at the other end of the condenser. Joints are made gas-tight, the air is exhausted from the apparatus and the distillation commenced. The boiling point of a liquid varies with the pressure of the atmosphere, and the temperature at which it boils falls with diminishing pressure. The constituents of oil of copaiba, in common with those of most volatile oils, decompose at the high temperature at which they boil under atmospheric pressure but, if distilled *in vacuo*, the constants of the oil are unaltered by the lower temperature involved, although the delicate aromas may be impaired. The optical rotation of the oil thus obtained from genuine copaiba should lie between $-7°$ and $-35°$. If this oil is redistilled *in vacuo* the first 10 per cent. should have a slightly greater lævo-rotation than the original oil, indicating that the material under examination is free from African copaiba which is dextro-rotatory and would cause the rotation of the first 10 per cent. to be less than that of the original oil. Gurgun balsam, or wood oil, is another oleo-resin which has sometimes been employed as an adulterant of copaiba, but its presence is readily revealed by the production of a red or purple colour when 4 drops of the volatile oil separated from the sample by distillation *in vacuo* is added to a mixture of 1 drop of concentrated nitric acid and 3 ml. of glacial acetic acid.

Fig. 5.—THE BRITTLE NATURE OF THE RESIN FROM COPAIBA

Showing the splintering caused by tapping the under-surface of nickel dish with a lead pencil.

Only the resin of copaiba is diuretic, but the oleo-resin is especially used in chronic inflammation of the genito-urinary tract both for its mildly stimulant action upon the inflamed mucous membrane and for its antiseptic properties. Owing to its disagreeable taste it is usually administered in gelatin capsules, but is sometimes given in the form of an emulsion made with mucilage of acacia.

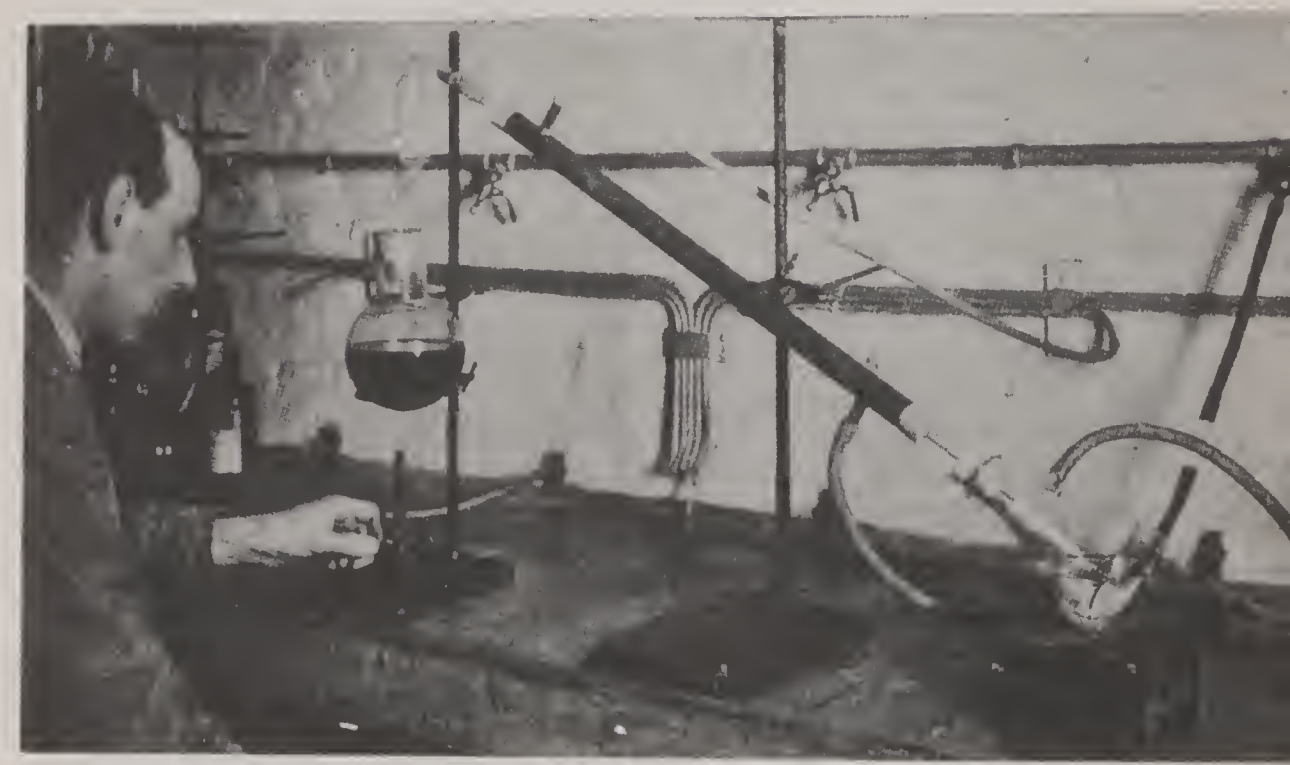


Fig. 6.— DISTILLATION OF COPAIBA UNDER REDUCED PRESSURE IN ORDER TO SEPARATE THE VOLATILE OIL FOR EXAMINATION

PAREIRA ROOT

This drug is derived from a lofty climbing shrub with long woody stems and leaves as much as a foot in length, which grows in Peru and in the neighbourhood of Rio de Janeiro in Brazil. The plant bears bunches of oval, black berries about 2 cm. long, resembling grapes in appearance, whence the Portuguese missionaries, who visited Brazil in the seventeenth century and heard of its medicinal virtues, gave it the name of *Pareira Brava* or Wild Vine. Daniel Hanbury, who was studying this drug about the year 1870, considered the plant from which it originated to be *Chondrodendron tomentosum*, and it is so described in the British Pharmacopœias of 1885 and 1898. However, among pharmacognosists, there has always been some doubt as to the accuracy of this conclusion and recently the subject has been further investigated by Harold King, who has found that the so-called *Pareira Brava* comes from two species known as *Chondrodendron platyphyllum* and *C. microphyllum*, plants whose taxonomical characters are very similar. There is no apparent difference in the pharmacognostical character of their roots, but Harold King has observed the remarkable fact that *C. platyphyllum* yields to chemical treatment an alkaloid bebeerine which is lævo-rotatory (turns the plane of polarised light to the left), whereas *C. microphyllum* contains dextro-rotatory bebeerine. Daniel

Hanbury records that in 1873 he was presented by G. B. Francis,* of Hearon, Squire and Francis (later amalgamated with others to form The British Drug Houses Ltd.), with two specimens of roots bearing some leaves and marked respectively *Pareira Brava*, large leaf, and *Pareira Brava*, small leaf, but that between the two roots he failed to recognise any difference. In the light of modern knowledge it appears that *C. tomentosum* does not occur in Brazil, whence all *Pareira Brava* comes to the market.

Pareira root is not now a drug of importance, and but for the above extraordinarily interesting discoveries would not have been given individual notice here. However, it acts as a diuretic and was formerly much favoured for the treatment of cystitis and kindred complaints; it was administered in the form of a decoction or as the liquid extract.

OTHER DIURETICS

A small number of vegetable drugs of minor importance which are occasionally used for the treatment of affections of the urinary tract remain to be mentioned and are listed in Table VII.

TABLE VII—VEGETABLE DRUGS OF MINOR IMPORTANCE HAVING DIURETIC ACTION

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Remarks*
Boldo Leaves (Boldo Folia)	Leaf ..	Tincture ..	Derived from an evergreen tree growing in the central provinces of Chili. The drug is fairly widely used in South America.
Collinsonia (Collinsonia)	Rhizome	Tincture ..	Contains a glucosidal saponin and resin: the latter when isolated is called Collinsonium.
Cubebs (Cubebæ Fructus)	Fruit ..	Oleo-resin (in gelatin capsules) and Tincture	Contains 10 to 18 per cent. of volatile oil and also resin. The oleo-resin is an ether extract of the fruit.
Kava (Kavæ Rhizoma)	Rhizome	Liquid Extract	Used as an antiseptic and diuretic in gonorrhœa and cystitis. A solid extract is given in capsules with oil of sandalwood.
Matico (Matica)..	Leaf ..	Infusion and Tincture	A urinary antiseptic used for cystitis, gonorrhœa and catarrh of the bladder. The Tincture is used as a styptic for cuts.

* Mr. G. B. Francis was a Director of The British Drug Houses Ltd. from the date of its inception in 1908 until his retirement in 1922. He was born in 1850 at the famous house of John Bell & Co., 338, Oxford Street, London, and died at Little Marlow in 1929. The present author remembers with gratitude many a kindly word by which Mr. Francis encouraged him in the early days of struggle.

EMMENAGOGUES

Substances classified under this heading stimulate and help to regulate menstruation. In this connection vegetable drugs are of little importance since much more effective treatment is now available in the shape of the various sex hormones which are derived from animal sources or, in certain instances, are prepared synthetically. Aloes, which has already been discussed, besides its primary action as a purgative, is generally considered to be of value in the treatment of amenorrhœa (absence of menstruation) and in oligomenorrhœa (inadequate flow). A selection of drugs of vegetable origin which have been employed for their supposed value as emmenagogues is given in Table VIII.

Besides the drugs noted in the table certain volatile oils are employed as emmenagogues, among which may be mentioned Oil of Pennyroyal, Oil of American Pennyroyal (Oil of Hedeoma) and Oil of Parsley, while gin owes its popularity as a domestic remedy to the Oil of Juniper it contains.

TABLE VIII—VEGETABLE DRUGS EMPLOYED AS EMMENAGOGUES

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Remarks*
Aletris Rhizome or Starwort (Aletridis Rhizoma)	Rhizome ..	Liquid Extract	Obtained from *Aletris farinosa*, a small herb growing in the United States.
Apiol (Apiol)	Ether Extract from fruit of parsley	—	Usually administered in capsules or perles.
Black Haw (Viburnum)	Bark ..	Liquid Extract and Compound Elixir	The Compound Elixir contains, in addition, hydrastis: it is used for dysmenorrhœa and to arrest threatened abortion.
Black Hellebore (Helleborus)	Rhizome ..	Tincture ..	A powerful cathartic. Contains two toxic glucosides and is rarely used.
Calendula or Marigold Florets (Calendula)	Florets ..	Tincture ..	The Tincture after dilution with water is also used as a lotion for sprains and bruises.
Canella or Wild Cinnamon Bark (Canellæ Cortex)	Bark ..	Powdered Aloes with Canella (Hiera Picra)	The chief constituent is about 1 per cent. of a volatile oil.
Caulophyllum or Blue Cohosh (Caulophyllum)	Rhizome and Roots	Liquid Extract and Compound Solution of Caulophyllum and Pulsatilla	Contains a glucoside, leontin, and an alkaloid, caulophylline; also resins known in the isolated form as Caulophyllin and sometimes administered in pill form.

TABLE VIII—VEGETABLE DRUGS EMPLOYED AS EMMENAGOGUES — *continued*

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Remarks*
Cimicifuga or Black Cohosh (Cimicifugæ Rhizoma)	Rhizome and Roots	Liquid Extract and Tincture	Cimicifugin is the isolated resinous constituent. Tincture of Cimicifuga is sometimes given with Tincture of Gelsemium for neuralgia (see page 89).
Cotton Root Bark (Gossypii Radicis Cortex)	Root Bark	Liquid Extract and Decoction	The chief constituent is a pale yellow resin.
Pulsatilla (Pulsatilla)	Whole Herb	Tincture ..	The active constituent has vesicant properties and is called Anemonin.
Rue (Rutæ Herba) ..	Whole Herb	Infusion ..	The volatile oil, of which the herb contains about 0·06 per cent., is sometimes given as a carminative in hysteria.
Savin (Sabina) ..	Young Shoots	Liquid Extract and Compound Elixir	The Compound Elixir contains, in addition, hydrastis: it is used for dysmenorrhœa and to arrest threatened abortion.

APHRODISIACS

Aphrodisiacs are substances which possess the power to stimulate the genital organs. Only a very few vegetable drugs can be regarded as possessing a direct influence on the sexual functions and the use of these is now being displaced by the recently discovered sex hormones. Nux vomica, and the alkaloid strychnine derived from it, are credited with value as aphrodisiacs but their action on the genitilia is only incidental, since *Strychnos* alkaloids, by their characteristic action on the central nervous system, stimulate almost all the reflexes of the body. Among drugs derived from vegetable sources the only important aphrodisiac is the alkaloid yohimbine, sometimes called corynine, and the origin of this alkaloid merits separate notice.

YOHIMBE

Yohimbe is the bark of *Pausinystalia yohimba*, a tree belonging to the Natural Order Rubiaceæ, which is indigenous to the Cameroons and the French Congo. It usually occurs in commerce in channelled pieces from 2 to 20 mm. thick, the outer surfaces being longitudinally furrowed and the greyish-brown colour being variegated with a tinge of red. The chief constituent is the alkaloid yohimbine, also known as corynine

The bark contains, in addition, other alkaloidal substances, allied to yohimbine, including isoyohimbine, dihydroyohimbine, alloyohimbine and yohimbene. The total amount of alkaloid present in the dried bark varies from 0·3 to 1·5 per cent.

YOHIMBINE HYDROCHLORIDE

Yohimbe serves as the source of yohimbine hydrochloride in which form the drug is employed for medicinal purposes. The pure alkaloidal salt may be prepared by treating the mixed ether-soluble alkaloids of yohimbe with an alcoholic solution of hydrochloric acid and triturating the resinous mixture of hydrochlorides so precipitated with acetone. The crude hydrochloride thus obtained can then be purified by crystallisation from hot water or alcohol. It occurs as a white, odourless, crystalline powder having a bitter taste.

Yohimbine hydrochloride is employed in the form of an aqueous solution either hypodermically or orally as a remedy for sexual impotence, particularly in veterinary practice. It possesses an advantage over strychnine in that the stimulation produced acts selectively on the pelvic reflexes. Pills and tablets containing yohimbine hydrochloride are also used for oral administration.

DAMIANA

This drug consists of the leaves of a herb, *Turnera diffusa*, which is indigenous to south-western Texas and Mexico. The light green, broadly lanceolate leaves are 10 to 25 mm. long by 5 to 10 mm. wide. The chief constituents are 0·5 to 1 per cent. of a greenish coloured volatile oil, having an odour resembling that of chamomile flowers, and a light amorphous bitter principle termed damianin. Damiana is a mild purgative and, if its reputed value as an aphrodisiac has any foundation in fact, the effect is probably associated with the mildly irritant nature of the volatile oil which may induce increased peristalsis and gentle stimulation of the genito-urinary tract during its excretion. A dry extract is sometimes prescribed in pill form and a compound pill containing the same preparation of damiana together with phosphorated suet and dry extract of nux vomica is used as a general tonic.

Chapter XIII

CARMINATIVES

THIS term is applied to a group of aromatic drugs which induce a gentle irritation to the alimentary tract and thus afford a sense of well-being and comfort to the patient. When administered they often encourage the appetite and relieve any feeling of distension by promoting the eructation of gas. A large number of volatile oils possess this property and most of the carminative vegetable drugs, with the important exception of ginger, owe their action to the oil they contain. Thus coriander is an important constituent of confection of senna and is included to relieve intestinal flatulence and thus minimise the pain and griping induced by the action of the purgatives.

Carminatives are frequently incorporated into medicines by diluting to volume with the appropriate water of the drug as a substitute for ordinary distilled water. These aromatic waters are prepared by adding, say, 20 parts of ordinary water to 1 part of the drug and distilling 10 parts. However, it is more usual to use concentrated waters made by dissolving the appropriate volatile oil in 90 per cent. alcohol and cautiously diluting with water until the alcoholic strength is reduced to about 55 per cent. by volume ; these preparations are regarded as being forty times stronger than the distilled aromatic waters and for dispensing purposes it is customary to dilute 1 part with 39 parts of plain distilled water. Distilled peppermint water, which is one of the most important of the carminatives, constitutes an exception, since this is made by mixing 1 ml. of oil of peppermint with 1500 ml. of plain distilled water and distilling 1000 ml. while, at the same time, a preparation forty times as strong and containing alcohol is usually employed in dispensing practice.

Volatile, or essential oils, as their name implies, are oily substances which readily volatilise on heating. They are usually highly odoriferous and the majority of them are isolated from plants by distillation processes. Most of them consist of complicated mixtures of organic chemical compounds of diversified character. Many contain unsaturated hydrocarbons termed terpenes, all having the general formula $C_{10}H_{16}$ but differing among themselves in molecular structure. Besides the terpenes proper, there are other hydrocarbons known as sesquiterpenes with the empirical formula $C_{15}H_{24}$. Among the most important constituents of medicinal volatile oils are the oxygenated compounds which include various acids, esters, aldehydes, alcohols, phenols, ketones, oxides and peroxides.

From the foregoing it will be understood that isolated volatile oils are more generally used as carminative medicines than the original vegetable drugs and, therefore, it will only be necessary here to offer notes on examples in which the original plant material is used directly.

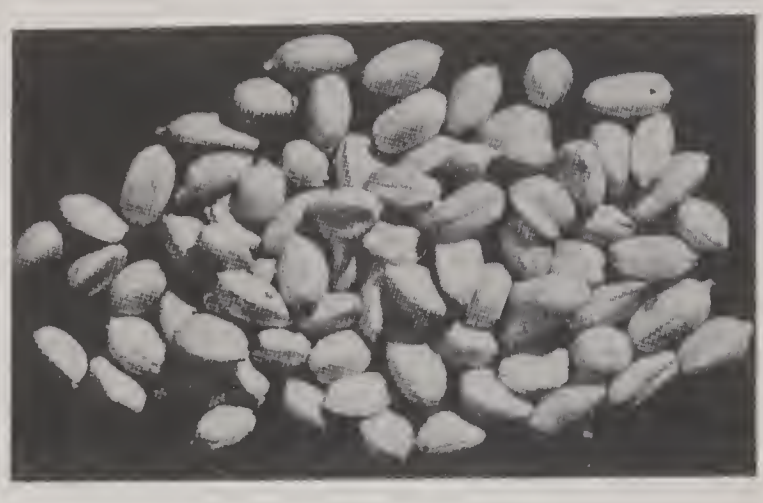


Fig. 1.—CARDAMOM FRUIT

This picture shows the whole capsules which are imported in cases each holding 84 lb.

CARDAMOM

The official drug consists of the dried and nearly ripe seeds of *Elettaria Cardamomum.* Cardamom of commerce is derived from plants cultivated in Southern India and Ceylon. The fruit, which is capsular, is cut from the plants just before it has ripened and before the seeds have been discharged. The cream or nearly white fruits are usually somewhat elongated and vary from 1 to 2 cm. in length. The interior of the fruits is divided into three cells, each containing two rows of dark reddish-brown, irregularly angular seeds about 3 mm. in length and strongly marked with transverse wrinkles. The seeds have an aromatic odour and pungent taste, but the capsules, or pericarps, are quite odourless. It is customary to keep the seeds in the capsules until required for use.

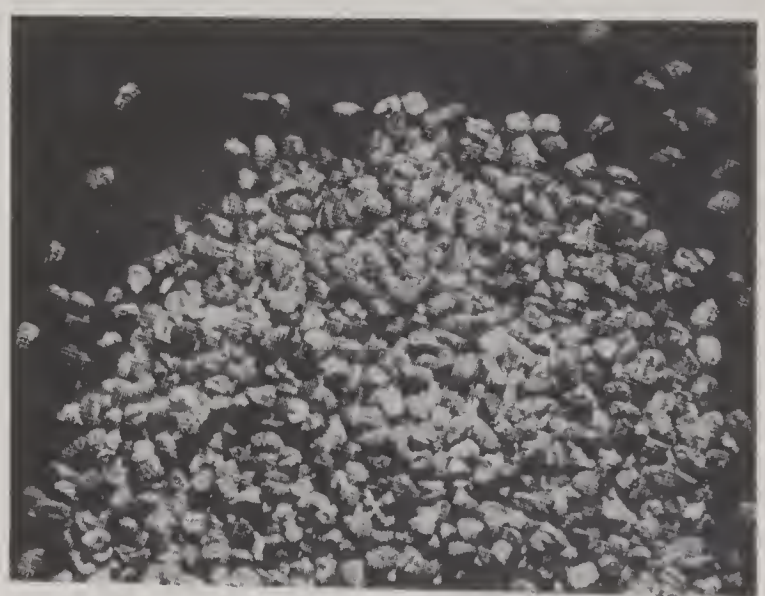


Fig. 2.—CARDAMOM SEEDS

The transverse wrinkles, characteristic of this seed, are clearly shown.

Chemistry of Cardamom

The most important constituent is the volatile oil, the amount of which varies from 2 to 7 per cent. This oil contains the ester, terpinyl acetate, and the

corresponding alcohol, terpineol. There is also present a small proportion of cineole, which is considered to be an oxide and is the main constituent of eucalyptus oil. Limonene, a widely distributed terpene, is also present in cardamom oil. It may be mentioned that the seeds contain a considerable proportion of starch. The ash (mineral matter) should not exceed 6 per cent.

Pharmacy of Cardamom

By far the most important galenical made from cardamom is the compound tincture. This is prepared by mixing together equal weights of powdered cardamom seed and caraway fruit with cinnamon bark and cochineal, both in powder, moistening the mixture with 60 per cent. alcohol and percolating with the same solvent. The tincture is completed by incorporating 5 per cent. by volume of glycerin and should contain the extractive material from 1·4 per cent. of cardamom.

Carminative tincture is made by macerating 6·85 parts of bruised cardamom seeds in 75 parts of alcohol (90 per cent.) for 7 days and after decanting, and pressing the marc, adding to the resulting liquid strong tincture of ginger and about 1 part each of oil of caraway, oil of cinnamon and oil of clove the tincture being finally diluted with more alcohol to make 100 parts. Both preparations are prescribed in medicines for the relief of dyspepsia. The compound tincture is widely used as a colouring agent and also for flavouring purposes.

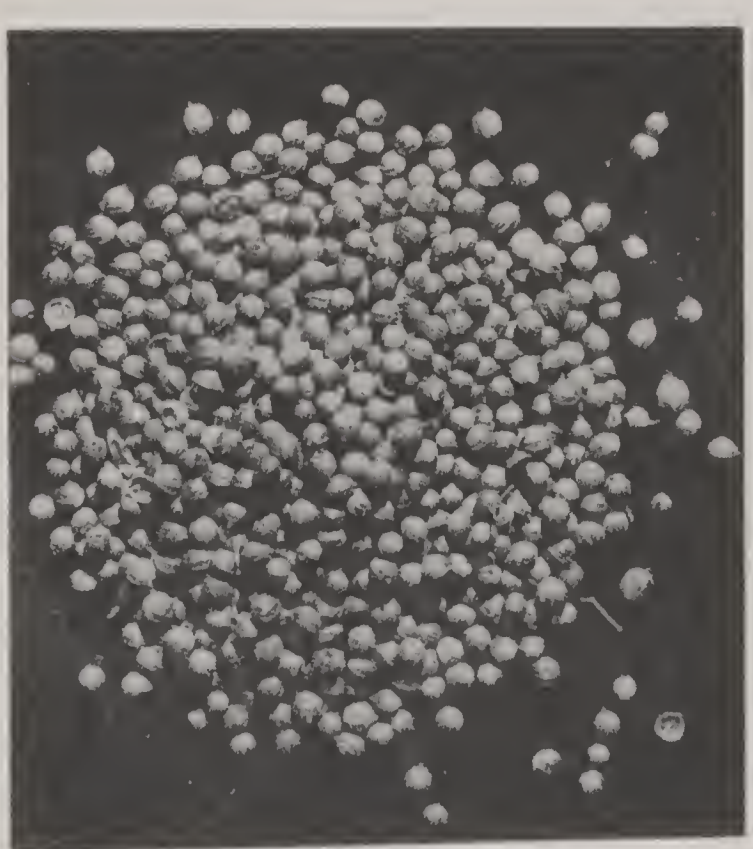


Fig. 3.—Coriander fruit

The remains of the sepals and styles can be seen surmounting some of the fruits.

CORIANDER

Coriandrum sativum is an annual herb cultivated in Russia, Thuringia, Moravia, Hungary and also in Northern Africa and India for the sake of its spicy fruit. As seen in commerce

the fruit consists of brownish-yellow, almost spherical bodies, about 3 mm. in diameter, often crowned by the remains of sepals and styles. The fruit possesses an aromatic odour.

Chemistry of Coriander

On distillation with steam the fruit yields up to 1 per cent. of volatile oil. Material which has been thus exhausted still contains about 17 per cent. of protein and 11 to 20 per cent. of fat and serves as fodder for animals. The principal constituent of the volatile oil is an alcoholic substance termed coriandrol. When this body is submitted to oxidation it yields citral, which is one of the most important constituents of lemon oil. The remainder of the oil consists of the terpenes, pinene and terpinene, together with traces of the alcohols, gerianiol and borneol. Volatile oil of coriander should be completely soluble in three times its volume of 70 per cent. alcohol. The mineral matter in coriander fruit should not exceed 7 per cent. and there should not be more than 1 per cent. of acid-insoluble ash.

Pharmacy of Coriander

Coriander is used pharmaceutically in association with purgative medicines to diminish their tendency to cause griping. Thus, it is an important constituent of confection of senna and for the same reason it is used in the preparation of compound tincture of rhubarb. Both these galenicals have already been described (see pages 115 and 113).

Fig. 4.—JAMAICA GINGER

The fibrous nature of the drug is apparent from this picture, which shows three "hands." When imported, good ginger is always packed in casks or kegs, each holding about 1¼ cwt.

GINGER (ZINGIBER)

This is probably the most important of the aromatic group of drugs. It consists

of the dried rhizome of *Zingiber officinale* and is known in pharmacy as Zingiber. The plant consists of aerial stems about a metre high which spring from the branching rhizomes, or subterranean stems, which carry the roots. It is a native plant of Asia but is successfully cultivated in the West Indies, Africa and Japan. When the aerial parts have withered, the rhizomes are dug up, washed, peeled with a knife, again washed and finally dried in the sun. Some commercial ginger still retains the cork layer and is described as " unpeeled." In order to impart a pleasing appearance ginger is often bleached with sulphurous acid or chlorine, or it may be " limed " by treatment with calcium sulphate or chalk. The British Pharmacopœia specifies that the drug is to be unbleached. It occurs as flattened branched pieces termed " races " or " hands " averaging about 9 cm. in length. The shapes assumed by these pieces, while characteristic, are difficult to describe and their appearance is best appreciated by reference to Fig. 4 which depicts the official Jamaica drug.

Varieties of Ginger

The principal commercial varieties are known as Jamaica, Cochin and African. The " hands " of Cochin ginger are smaller and less branched than those derived from Jamaica. The African variety is darker in colour, not so carefully prepared, and also retains the covering of cork ; it is exceedingly pungent but does not possess the fine aroma characteristic of Jamaica ginger.

Chemistry of Ginger

The drug contains from 1 to 3 per cent. of a viscid greenish-yellow volatile oil which is responsible for the aroma but not for the pungency of ginger. The oil largely consists of a sesquiterpene called zingiberene together with traces of another sesquiterpene called bisabolene, which is widely distributed in volatile oils. Oxygenated constituents have also been identified including cineole, citral and borneol.

The pungent properties of ginger are attributable to the presence of gingerol, a yellowish oily substance possessing phenolic properties. It dissolves in warm aqueous solution of potassium hydroxide and at the same time loses its pungent property.

Determination of Gingerol

The amount of pungent principle may be determined by the following method worked out by H. Garnett and J. Grier : Ten gm. of the finely powdered drug is dried at 100° C. for about half an hour, then transferred to a Soxhlet extraction apparatus (see page 124) and extracted for

2 hours with anhydrous ether. This removes the gingerol together with other material. The solvent is distilled off, the residue treated with boiling petroleum spirit and the resulting solution filtered into a separating funnel. The extraction of the residue with petroleum spirit is repeated two or three times, the extracts being added to the first portion in the separating funnel. The petroleum, containing the gingerol, is now extracted by shaking with several portions of 60 per cent. alcohol. The latter solvent is immiscible with petroleum, and, after the liquids have been agitated, separates as the lower layer and is then drawn off into a flask. Most of the alcohol is now evaporated and the residual liquid again transferred to a separating funnel and extracted with several portions of ether, the latter being run into a tared flask. After removing the ether by distillation and drying at 80° C. the flask, containing the pure gingerol, is weighed. By this process a good sample of Jamaica ginger yields about 1 per cent. of gingerol, while 2 per cent. may be obtained from the more pungent African variety.

Tests for Purity

The alcohol-soluble extractive matter using 90 per cent. alcohol should not be less than 4·5 per cent. and the water-soluble extractive not less than 10 per cent. These determinations are carried out by the methods already described (see page 13). The ash should not exceed 6 per cent. and the water-soluble ash should not be less than 1·7 per cent. The determination of the water-soluble ash is important since a value less than the stated limit points to the presence of exhausted or "spent" ginger. All these specifications apply to the official Jamaica drug.

The Test for Sulphites

As already stated, the British Pharmacopœia stipulates that ginger must not be chemically bleached and consignments must therefore be examined for the presence of sulphites. This is conveniently carried out by employing the method advocated in Report No. 43 on Public Health and Medical Subjects issued by the Ministry of Health. For routine testing the procedure may be simplified by using the apparatus illustrated diagrammatically in Fig. 5. The determination depends upon the fact that when material which has been bleached with sulphites is boiled with dilute hydrochloric acid, sulphur dioxide gas is evolved, which is carried by means of a current of carbon dioxide through the condenser into absorption tubes containing neutral hydrogen peroxide which immediately oxidises the sulphur dioxide to sulphuric acid. The acid formed is then titrated with standard sodium hydroxide.

To conduct a determination, 500 ml. of water and 20 ml. of hydro-

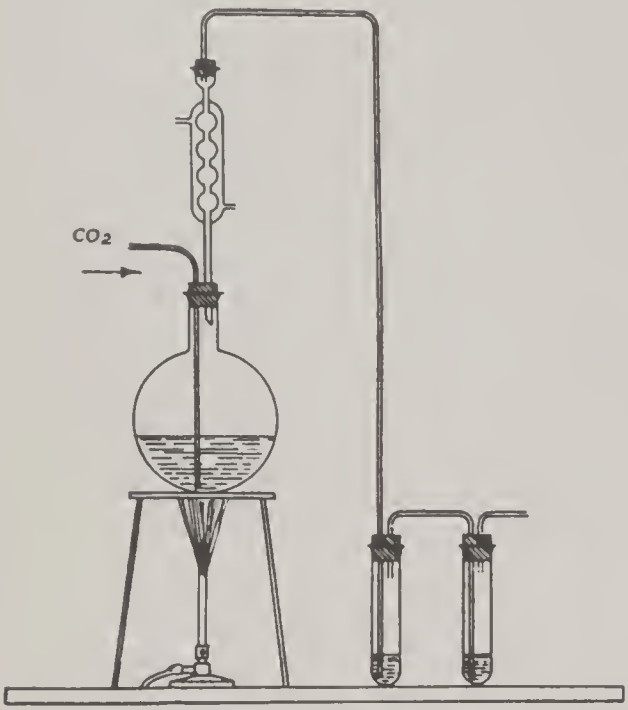


Fig. 5.—Apparatus for the determination of sulphites in ginger

The drug is treated in the large flask with boiling dilute hydrochloric acid and any sulphur dioxide evolved reacts with the hydrogen peroxide contained in the absorption tubes forming sulphuric acid, which is then titrated with standard sodium hydroxide.

chloric acid are introduced into the flask and 10 ml. of hydrogen peroxide (10 vols.), previously neutralised to bromo-phenol blue indicator, is added to each absorption tube. The apparatus is connected up and a stream of carbon dioxide, previously bubbled through sodium carbonate solution, is passed in while the dilute acid is heated to boiling. After boiling has continued long enough to remove air, the flask is cooled by running a stream of cold water over the outside, the stopper is removed, 100 gm. of coarsely powdered ginger quickly introduced and the stopper replaced. The mixture is gently boiled for at least 45 minutes, the absorption tubes are then disconnected and their contents titrated with decinormal sodium hydroxide, using bromo-phenol blue as indicator. Each ml. of decinormal sodium hydroxide required is equivalent to 0·0032 gm. of sulphur dioxide. In the absence of sulphites in the ginger no acidity will have developed.

Pharmacy of Ginger

Ginger is a carminative and gastric stimulant and is widely employed in the treatment of dyspepsia, as well as being useful for correcting the griping tendency of purgative medicines. Tincture of ginger is prepared by treating the powdered drug with alcohol by the standard percolation process. This galenical is made in two different concentrations, two parts of the strong tincture representing one part of the drug, while the weaker preparation is a 1 in 10 tincture.

Syrup of ginger, which consists of a mixture of simple syrup and the strong tincture, is a useful carminative flavouring agent, and serves as a vehicle for the administration of other drugs.

Oleo-resin of ginger, or gingerin, is prepared by percolating powdered ginger with acetone until completely exhausted, distilling off most of the solvent from the percolate and drying the residue on a water-bath until it forms a brownish mass of syrupy consistency. This preparation, which should not be confused with the natural oleo-resins, is used for a variety of purposes including the manufacture of pills and tablets.

Compound ginger tablets, or ginger mint tablets, represent the type of medicament containing ginger which is prescribed for indigestion. Each tablet contains about an eighth of a grain of gingerin together with 5 gr. of sodium bicarbonate, ammonium carbonate and a little oil of peppermint. In making the tablets a small quantity of powdered gum acacia is added and the mixture, consisting of all the ingredients except the ammonium carbonate, is granulated with theobroma emulsion and, after drying, the ammonium carbonate is added and the mixture compressed into tablets. Theobroma emulsion contains 25 per cent. of oil of theobroma, 2·5 per cent. of hard soap and 0·57 per cent. of powdered tragacanth emulsified with water. A little benzoic acid is added as a preservative.

The Detection of Capsicum in Ginger Beverages and Galenicals

The extremely pungent drug capsicum has been used to adulterate preparations made from partially exhausted ginger. The following procedure serves as a delicate test for the presence of capsaicin which is the pungent principle of capsicum :

If alcohol is present in the preparation it is evaporated off and the residual liquid transferred to a separating funnel and extracted with ether, which dissolves both gingerol and capsaicin. The ethereal solution is transferred to a dish and about 10 ml. of 10 per cent. alcoholic solution of potassium hydroxide added and the mixture evaporated to dryness on a water-bath. A suspension consisting of about 6 mg. of powdered manganese dioxide in 15 ml. of water is now added and the heating continued until all volatile oil is dissipated. After cooling, the residual liquid is acidified with dilute sulphuric acid, the mixture is transferred to a separating funnel and agitated with about 10 ml. of petroleum spirit. After separation, the lower aqueous layer is rejected and the petroleum evaporated to dryness in a small dish. This treatment destroys gingerol but does not affect any capsaicin which may be present. Hence by applying to the tip of the tongue the residue left after evaporation of the petroleum any pungency due to adulteration with capsicum is at once perceived.

VALERIAN

This drug is the dried rhizome and roots of *Valeriana officinalis*, a herb well known in this country and common throughout Europe and

Northern Asia. It is cultivated in England and on the Continent for the sake of its medicinal properties.* As seen in commerce the drug consists of short yellowish-brown conical-shaped rhizomes about 2·5 cm. long to which numerous slender roots are attached which average about 7 cm. in length. Valerian possesses a powerful and disagreeable odour while the taste is officially described as being "sweetish, camphoraceous and slightly bitter."

Chemistry of Valerian

The drug contains about 1 per cent. of a brownish-yellow volatile oil. On keeping, the colour darkens and the oil becomes viscid. The principal constituent of the oil is about 10 per cent. of the ester, bornyl isovalerianate, the remainder consisting chiefly of the terpenes, camphene and pinene, together with about 1 per cent. each of the bornyl esters of formic, acetic and butyric acids. The characteristic odour of the drug is due to the gradual formation of free isovalerianic acid from the bornyl isovalerianate. It has been stated that valerian root derived from Mexico contains free isovalerianic acid but does not yield any volatile oil.

Fig. 6.—VALERIAN RHIZOME AND ROOT

The drug also contains two alkaloids named chatinine, and valerine or valerianine. The former is soluble in ether, but valerine is insoluble though easily dissolved by chloroform. Valerian contains about 0·1 per cent. of total alkaloids of which about three-quarters consists of chatinine. These bodies do not appear to possess any great physiological activity, and therefore cannot be considered as the therapeutic active principles of the drug.

Besides the oil and the alkaloids, valerian contains resinous bodies which are thought to be partly responsible for the medicinal action of the drug.

Apart from the estimation of the volatile oil, no satisfactory method for evaluating valerian has been devised. A complicated process of assay, aiming at the separate determination of the volatile oil and the

* This should not be confused with *Centranthus ruber*, or spur valerian, commonly cultivated in gardens.

resins, has been proposed but it will not be described here since there is still doubt as to what constituents of the drug are pharmacologically desirable.

Pharmacy of Valerian

Valerian possesses the carminative action characteristic of this group of volatile oil drugs but it is mainly employed as a nervine stimulant to the digestive organs. The benefits accruing from its administration have commonly been attributed to the mental impression produced by its strong odour and taste and not to any action it produces after absorption. This observation, however, requires confirmation.

The drug is generally administered with ammonia, and ammoniated tincture of valerian is the most important galenical. It is prepared by treating powdered valerian by the standard maceration process with a solution consisting of 9 volumes of 60 per cent. alcohol mixed with 1 volume of 10 per cent. ammonia solution and small quantities of oils of nutmeg and lemon. Five parts of the completed tincture contains the extractive material of one part of valerian.

An extract of valerian for incorporation into pills is prepared by percolating the powdered drug with 70 per cent. alcohol and evaporating the percolate until a firm pilular extract is obtained.

CINNAMON

The small evergreen cinnamon tree, richly clothed with beautiful glossy leaves, is a native of Ceylon, whence the bark, which constitutes the official drug, is obtained. It occurs as single or double, closely packed compound quills, up to a metre or more in length, about 1 cm. in diameter, dull pale brown in colour and extremely thin, often being marked with little scars or holes. The drug has a fragrant odour and warm sweet aromatic taste. It contains 0·5 to 1 per cent. of volatile oil, which consists largely of cinnamic aldehyde, and, in addition, appreciable proportions of tannin and mucilage.

Apart from its value as a carminative, cinnamon possesses some virtue as an intestinal astringent for the treatment of diarrhœa. For this purpose compound powder of cinnamon is a useful preparation ; it contains, in addition, cardamom seeds and ginger, all three constituents being present in equal proportions. The tincture, which is a 1 in 5 preparation made by the percolation process with 70 per cent. alcohol, is used as a carminative. Besides its application as a drug, powdered cinnamon bark is widely employed as a spice for purposes of food flavouring.

CHAMOMILE FLOWERS (ANTHEMIDIS FLORES)

The material employed medicinally consists of the dried flower-heads derived from a cultivated variety of *Anthemis nobilis*, a composite plant indigenous to Great Britain. The flower-heads form hemispherical masses from 1 to 2 cm. in diameter, the yellow disc florets of the wild plants having been mostly changed into white ligulate florets. The drug possesses a strong aromatic odour and bitter taste. The constituents include 0·8 to 1 per cent. of volatile oil, a crystalline bitter glucoside called anthemic acid, together with wax, fatty oil and glucose.

The drug is used internally in the form of a 1 in 20 infusion (chamomile tea) to improve the appetite and aid digestion while a 1 in 1 liquid extract made with 70 per cent. alcohol is employed as a carminative and bitter. If chamomile tea is taken while hot it acts as an emetic. The flowers are also used externally as a hot poultice for the treatment of abscesses and inflammatory conditions.

CLOVE (CARYOPHYLLUM)

Like numerous other vegetable drugs, clove was known to the ancients and it is recorded that it was in use in China during the Han dynasty (266 B.C. to A.D. 220) when it was customary for the court officials to hold the spice in their mouth before addressing the sovereign in order that their breath might have an agreeable odour. Readers will be familiar with the appearance of the reddish-brown dried flower buds of *Eugenia aromatica* in view of their use as a flavouring agent for culinary purposes.

Clove contains from 15 to 20 per cent. of volatile oil and about 13 per cent. of gallotannic acid whence it behaves both as a carminative and mild astringent. A fresh infusion and the corresponding concentrated infusion are included in the British Pharmacopœia 1932 ; these preparations, as well as clove water, are useful ingredients for inclusion in stomachic mixtures for the treatment of indigestion.

DILL (ANETHUM)

Dill water is a valuable remedy for the flatulence of infancy, and the preparation distilled from the fruit as well as its complement, the concentrated variety made directly from the volatile oil, are both official preparations of the Pharmacopœia. Dried ripe dill fruit is derived from *Anethum graveolens*, an annual herb cultivated in Germany and also to a smaller extent in England. Each of the brown mericarps, which are usually separate in the commercial drug, is about 4 mm. long and 2 to 3 mm. broad. They are so strongly compressed as to be almost flat, and the lateral ridges are prolonged to form membranous wings, the dorsal ridges being brown in colour and consequently inconspicuous. They have a pleasant aromatic odour and taste, mainly due to the 3 or 4 per cent of volatile oil which the drug contains.

NUTMEG (MYRISTICA)

The appearance of the dried kernels of the seeds of *Myristica fragrans*, which constitute the nutmeg of commerce, is familiar to most people. The seeds are derived from a tree indigenous to the Molucca Islands and cultivated in Penang, Sumatra and the West Indies. The fruit resembles a small peach, which, as it ripens, splits and discloses the seed surrounded by a bright crimson reticulated arillus. This, when stripped off and dried, becomes dull reddish-yellow in colour and the product constitutes mace. Nutmeg, which contains from 8 to 15 per cent. of volatile oil and about 40 per cent. of solid fat, is a constituent of the official aromatic powder of chalk which in its turn is used in the preparation of aromatic powder of chalk and opium.

OTHER CARMINATIVE VEGETABLE DRUGS

A further selection of drugs belonging to this class are listed in Table IX.

TABLE IX—CARMINATIVE VEGETABLE DRUGS OF SECONDARY IMPORTANCE

Name (Latin Name in Brackets)	*Part of Plant Used*	*Content of Volatile Oil per cent.*	*Principal Preparations*	*Remarks*
Anise or Aniseed (Anisi Fructus)	Fruit ..	1·5 to 3·5	Water ..	Spanish fruit is the finest, while that from S. Russia is used for the production of oil.
Black Pepper (Piper Nigrum)	Fruit ..	1 to 2·3	Confection ..	Contains about 6 per cent. of the alkaloid piperine. White pepper consists of the fruits deprived of the outer portion of the pericarp.
Caraway (Carum)	Fruit ..	3·5 to 7	Water ..	Used along with coriander for the preparation of Compound Tincture of Senna of the B.P. 1914.
Cassia Bark (Cassiæ Cortex)	Bark ..	1 to 2	—	Closely resembles cinnamon and is sometimes called Chinese Cinnamon after the country of its origin.
Cassia Buds (Cassiæ Flores)	Immature Fruit	*circa* 1·6	—	Consists of hard, club-shaped, brown or greyish immature fruits of the same tree that yields cassia bark and allied species.

TABLE IX—CARMINATIVE VEGETABLE DRUGS OF SECONDARY IMPORTANCE—*continued*

Name (Latin Name in Brackets)	*Part of Plant Used*	*Content of Volatile Oil per cent.*	*Principal Preparations*	*Remarks*
Cummin Fruit (Cumini Fructus)	Fruit ..	3 to 4	—	Used as a carminative in veterinary medicine.
Fennel (Fœniculum)	Fruit ..	4 to 5	Water ..	This drug is a constituent of Compound Powder of Liquorice.
Galangal (Galangæ Rhizoma)	Rhizome ..	Small quantity present	Infusion and Decoction	Cultivated in S.E. China and Hainan. Contains a pungent oily substance called Galangol.
Grains of Paradise or Guinea Grains (Paradisi Grana)	Seed ..	0·3	—	Employed in veterinary practice as a substitute for cardamom. In early days the drug was conveyed from tropical Africa to Tripoli and, being an esteemed product of an unknown region, was given its strange name.
Horseradish Root (Armoraciæ Radix)	Root ..	—	Compound Spirit	Contains potassium myronate and myrosin, whence allyl isothiocyanate (Mustard Oil) is produced.
Oliver Bark or Black Sassafras (Oliveri Cortex)	Bark ..	1	Tincture (1 in 10, using 60 per cent. alcohol)	Obtained from *Cinnamomum oliveri*, a tree indigenous to New South Wales and Queensland. Used in Australia as a substitute for Cinnamon.
Pimento or Allspice (Pimenta)	Fruit ..	3 to 4·5	Water ..	Similar in odour and therapeutic action to cloves. It is also called Jamaica Pepper.
Sassafras Root (Sassafras Radix)	Root ..	2	—	*Sassafras officinale* is a tree widely distributed over the eastern United States. The bark of the root contains 6 to 9 per cent. of volatile oil.
Star Anise Fruit (Anisi Stellati Fructus)	Fruit ..	5	—	The volatile oil is almost identical with that obtained from anise fruit for which the drug is used as a substitute in India.

Chapter XIV

BITTERS

PREPARATIONS of these drugs are largely used in therapeutics in order to increase the appetite, and their administration is often followed by a distinct improvement in the digestion. This is the result of an increase in the secretion of gastric juice, due, not to any direct action on the gastric mucous membrane, but to a psychical reflex effect caused by the taste of the bitter substance. When bitters are introduced directly into the stomach they fail to exercise any improvement in the digestive response. It follows that the therapeutic value of these drugs is best elicited when they are given shortly before a meal and is attended with benefit only in cases in which the gastric juice is deficient. Improvement following the administration of bitters is largely subjective and, since these medicines are capable of producing a considerable impression upon patients, the effects may be due in part to suggestion rather than to any real action of the drug.

GENTIAN

Much the most important of the bitters, the name of this drug is said to originate from Gentius, an ancient king of Illyria, who first established its medicinal virtue. The name has been applied to a Natural Order of plants of which *Gentiana lutea*, a perennial herb

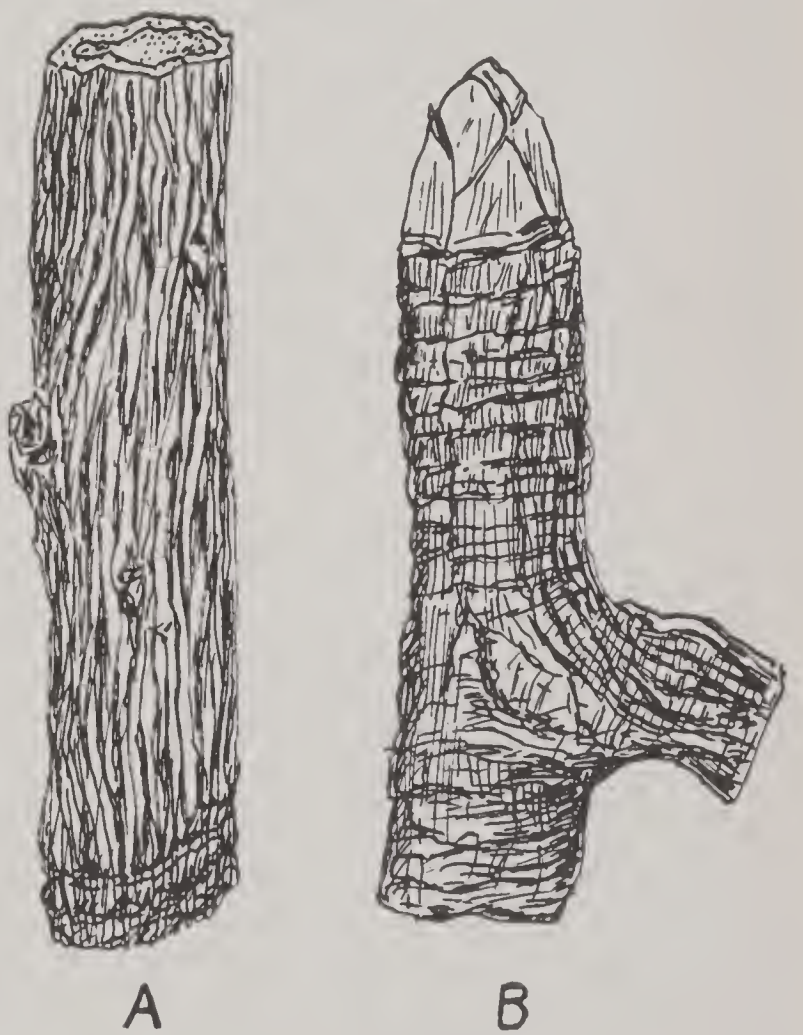


Fig. 1.—GENTIAN ROOT

A typical piece of root, showing longitudinal wrinkles, is seen at A, while B depicts the rhizome with bud and point of attachment of root.

indigenous to Central Europe, is the member identifiable as the source of gentian root. It occurs in yellowish-brown, longitudinally wrinkled, nearly cylindrical pieces 15 to 20 cm. long and about 2 cm. in thickness. The dried root is brittle, the fractured surface being of a reddish-yellow colour, but it becomes tough and flexible when moistened. Sometimes the cylindrical pieces are split longitudinally, or the drug may occur in commerce as transversely sliced pieces.

Dried gentian root contains the so-called bitter principles gentiin and gentiamarin ; another bitter constituent, gentiopicrin, is present in the fresh root but is hydrolysed by the fermentative changes which take place during the process of slow drying. In addition to these glucosidal substances, a yellow phenolic body, a trisaccharide sugar called gentianose as well as pectin are present. No satisfactory method of chemical evaluation is available and the ultimate criterion of quality rests on the question of flavour and degree of bitterness. However, the British Pharmacopœia specifies that the water-soluble extractive should not be less than 33 per cent. and that the ash should not exceed 6 per cent. The imposition of a lower limit of material soluble in water has an important bearing on the bitter quality of the drug since, during the slow drying of the root, unduly prolonged hydrolysis of the glucosides and fermentation of the gentianose present may take place with progressive diminution in the amount of water-soluble substances present in the root. On the other hand, slow drying is favoured with a view to preventing deterioration in colour and improving the aroma. Good gentian root yields about 40 per cent. to cold water, while highly fermented material may yield only a third as much.

Pharmacy of Gentian

Without doubt the most important galenical preparation is the official concentrated compound infusion. It is made by macerating for 48 hours with 25 per cent. alcohol a mixture of thinly sliced gentian, dried bitter-orange peel and lemon peel, both the latter being cut into small pieces. The liquid is pressed out, the marc macerated for 24 hours with more dilute alcohol and this second liquid expressed and added to the product of the first pressing ; the infusion is set aside for 14 days in order to allow for the separation of sediment and the preparation then completed by filtering. When diluted with seven times its volume of distilled water this concentrated infusion yields a preparation containing the extractive from 1·25 per cent. of root which is approximately equivalent in strength, but not in flavour, to fresh compound infusion of gentian. Since it does not contain any alcohol the latter must be used within 12 hours of its preparation, whereas the concentrated infusion may be stored indefinitely and is the variety almost invariably employed in practice. This galenical is widely used, being dispensed with liquid

extract of nux vomica, or solution of strychnine hydrochloride, and a little dilute hydrochloric acid to form an effective tonic. It is equally useful for dispensing with alkalis such as sodium bicarbonate and, in addition, is serviceable as a flavouring agent in mixtures containing potassium iodide or sodium salicylate.

Compound tincture of gentian is prepared by treating a mixture of the bruised root, dried bitter-orange peel and bruised cardamom seeds with 45 per cent. alcohol by the maceration process (see page 10). It is used as an aromatic bitter in medicines primarily designed for the relief of dyspeptic conditions.

Extract of gentian is made by adding to the crushed drug ten times its weight of water, infusing for 2 hours, boiling for 15 mins., decanting, pressing the marc and straining the expressed liquid and, after mixing the latter with the decanted liquid, evaporating to the consistency of a soft extract. This is sometimes used as a pill excipient, either alone or mixed with an equal weight of liquid glucose. From the foregoing considerations concerning the mode of action of bitters it will be realised that this preparation can have little real therapeutic value.

QUASSIA

This drug consists of the wood obtained from the trunk of a tree, *Picræna excelsa*, which is indigenous to Jamaica. The wood is imported in logs and for medicinal use is freed from bark, cut into chips and kiln dried. It is yellowish-white or bright yellow, tough but easily split; it has an intensely bitter taste but no odour.

The Chemistry of Quassia

The medicinally important constituents are the two crystalline bitter principles known as α-picrasmin and β-picrasmin. The wood also contains a very small quantity of a third crystalline bitter principle and a minute quantity of a yellow crystalline substance which exhibits a blue fluorescence in an acidified alcoholic solution.

It is possible to isolate α and β-picrasmin as a mixed crystallised product. This may be accomplished by exhausting the wood with 50 per cent. alcohol, neutralising with magnesia, acidifying with tartaric acid, removing the alcohol by distillation and extracting the residue with chloroform. The chloroformic solution is evaporated to a syrupy consistency, dissolved in a mixture of equal volumes of absolute alcohol and ether, the solution again evaporated, the residue dissolved in absolute alcohol, the solution covered with a layer of ether and set aside to crystallise. The separated crystals are finally purified by recrystallisation from alcohol. This product is known as crystalline quassin, but owing to its being only very slightly soluble in water it has little value medicinally.

Pharmacy of Quassia

The concentrated infusion is the most important galenical but it differs from the corresponding preparation of gentian in being simple and not compound. It is made by macerating rasped quassia with cold distilled water for 1 hour, straining and reserving the liquid, macerating the marc a second and a third time for 1 hour each with further portions of water. After the last maceration the marc is lightly pressed, the product of the second and third macerations is evaporated to low bulk, mixed with the liquid expressed from the marc, the product then mixed with the liquor from the first maceration, alcohol added and the volume of the whole suitably adjusted. After having been set aside for 14 days in order to allow sediment to separate the infusion is filtered. It is a 1 in 12·5 preparation of the drug and is officially required to contain between 21 and 24 per cent. by volume of alcohol. When diluted with seven times its volume of distilled water it yields a preparation which is approximately equivalent in strength, but not in flavour, to fresh infusion of quassia ; it differs also in containing a small proportion of alcohol which is added as a preservative.

The Pharmacopœia also includes a tincture which is a 1 in 10 preparation made with 45 per cent. alcohol by the maceration process. These two galenicals are employed in a similar way to the corresponding gentian preparations. Quassia is entirely free from tannin, hence it is a convenient bitter for dispensing with salts of iron.

CALUMBA

Calumba is the dried root of a climbing plant indigenous to Portuguese East Africa which grows abundantly in forests near the Zambesi. The drug occurs in commerce in flattish, irregularly circular slices depressed towards the centre, usually from 2 to 6 cm. in diameter and from 3 to 12 mm. in thickness and of a dull yellowish colour. The bitter constituents are mainly alkaloidal, three such substances having been characterised and named columbamine, palmatine and jateorhizine, the last two being so called from the botanical name of the drug, *Jateorhiza palmata*. These alkaloids are allied to berberine and, like that substance, are yellow in colour. In judging the quality of commercial consignments it is not usual to apply a determination of alkaloidal content, it generally being sufficient to rely upon pharmacognostical characteristics. However, the British Pharmacopœia imposes an ash limit of not more than 9 per cent., thus eliminating undue admixture of the dried rhizome of the plant which is inferior as a bitter and may yield from 12 to 17 per cent. of residue on incineration.

Pharmacy of Calumba

The principal galenicals are the concentrated infusion and the tincture, both being prepared similarly to the corresponding preparations of

quassia, but in the case of calumba more drug is required for making the infusion since 5 parts of the concentrated form are made from 2 parts of cut root. The proportions used for the tincture are the same as those employed for quassia but it is directed to be made with 60 per cent.

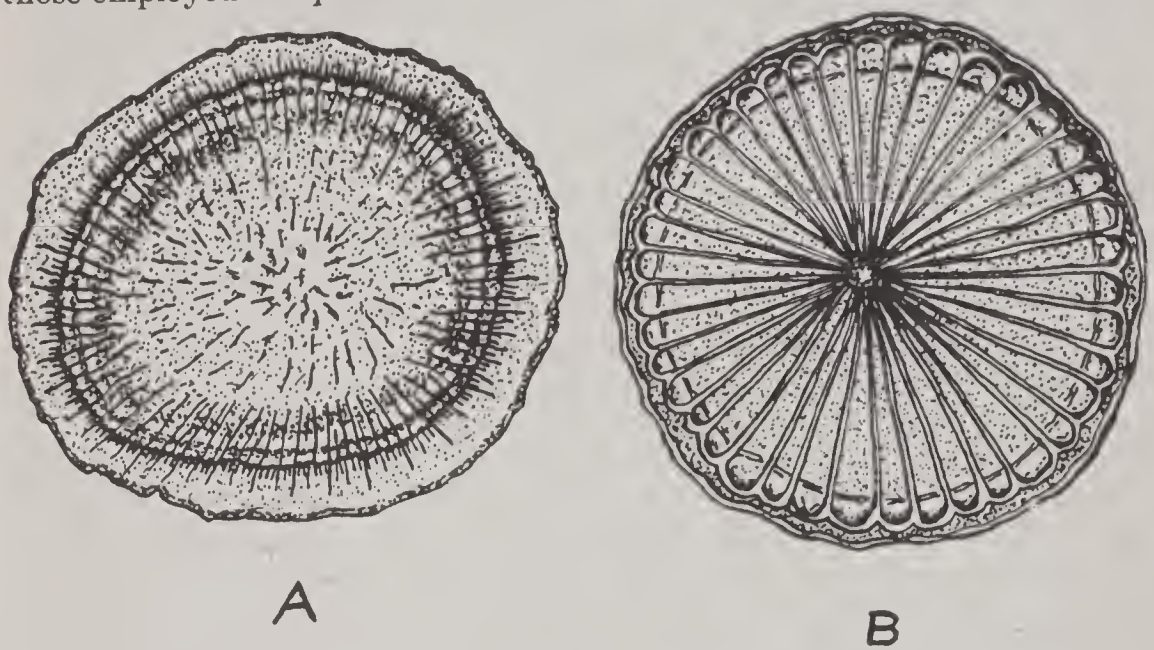


Fig. 2.—CALUMBA AND COSCINIUM

The transverse section of calumba root, A, shows the wrinkled corky layer, a thick bark marked with radiating lines of sieve tissue, and a central woody portion separated from the bark by a dark cambium line. The transverse section of the stem of *Coscinium fenestratum*, B, shows the numerous semi-lunar masses of phloem in the cortex, the wood, which consists of a single ring of wedge-shaped bundles containing many large vessels, and the small central pith.

alcohol. Calumba is used in the same way as gentian or quassia and it resembles the latter in being free from tannin and hence is useful for dispensing in mixtures containing iron.

SERPENTARY

The dried rhizome and roots of *Aristolochia reticulata*, a herbaceous plant growing in the United States, constitutes the drug known under this name and sometimes referred to as Texan serpentary. The rhizome is usually described as being about 2 cm. long and 2 to 3 mm. thick, bearing on its upper surface the remains of aerial stems and on its lower side numerous curved, but not matted, roots, often about 10 cm. long and from 0·2 to 1·2 mm. thick, the whole being of a dull yellowish-brown colour and possessing a camphoraceous odour. The bitter principle is stated to be alkaloidal in its chemical nature. It is used in the preparation of compound tincture of cinchona (see page 45), which is a highly important bitter tonic, and for this reason it is included as an official drug in the British Pharmacopœia 1932.

TARAXACUM ROOT

This is the root of the common dandelion, the name being derived from two Greek words, *Taraxos*, disorder, and *akos*, remedy, in allusion, of course, to its medicinal qualities. The word dandelion is said to be a corruption of the French *Dent-de-lion*, or lion's tooth, the reference being to the tooth-like lobes of the leaves. For pharmaceutical purposes the root is collected in the autumn and is used both in the fresh state and after drying. As first collected the root is yellowish-white but changes to a dark brown colour on drying, each piece being about 30 cm. in length and some 12 mm. or more in diameter. When the fresh material is broken a bitter, milky juice exudes from numerous circles of lacticiferous vessels.

The important constituents are the acid crystalline bitter principles taraxacin and taraxacerin and in addition there are various sugars and the carbohydrate inulin. Besides being a bitter, the drug is a mild laxative, but its medicinal virtue is not well exemplified in preparations made from the dried root. The most important galenicals are the extract and the juice, as prepared from the fresh root. Juice of taraxacum (Succus Taraxaci) is made by subjecting the bruised fresh root to pressure, adding to the expressed juice one-third its volume of alcohol, allowing the mixture to stand for 7 days and filtering. In order to prepare the extract, the expressed juice is heated at 100°C. for 10 minutes, then strained and evaporated to a soft, pasty consistency. The extract is sometimes administered with confection of senna or is included as a constituent of similar purgative mixtures. The preparation of the various galenicals using the dried root follow the usual methods, but as they are not so satisfactory from the therapeutic standpoint it will not be necessary to discuss them individually. Taraxacum is often employed by country people as a domestic remedy for dyspepsia, but the need for using the fresh root is a disadvantage and, since there are many alternative bitter drugs from which to choose, it may now be regarded as of minor importance.

CHIRETTA (CHIRATA)

This bitter consists of the whole dried plant *Swertia Chirata*, an annual herb indigenous to the mountainous districts of Northern India. When the flowering is well advanced the entire plant is collected, dried and packed into bundles which are sometimes compressed before exportation. The smooth, brown or purplish-brown stem is about a metre long and contains a continuous and easily separable pith. In the upper part it branches freely and bears numerous fruits and flowers and a few leaves. All parts of the drug have an intensely bitter taste.

Two bitter principles have been separated from the drug and called

ophelic acid and chiratin ; the latter, when treated with boiling dilute hydrochloric acid, yields ophelic acid and a substance which has been termed chiratogenin. The most important pharmaceutical preparations are the tincture, made with 60 per cent. alcohol by the percolation process (see page 10), and the concentrated infusion.

OTHER BITTERS

There are a number of other vegetable drugs belonging to this class which are only used occasionally or are employed in certain parts of the world as substitutes for the more important members of the group. A selection of these is listed in Table X.

TABLE X—VEGETABLE BITTERS OF SECONDARY IMPORTANCE

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Remarks*
Andrographis (Andrographis)	Whole Plant	Tincture (1 in 10 with 60 per cent. alcohol) and Concentrated Infusion	Used as the equivalent of chiretta in India and the East. Also known under the name "kreat."
Aristolochia (Aristolochia)	Stem and Root	Tincture (1 in 5 with 70 per cent. alcohol)	Used as the equivalent of serpentary in India and the East. It is *Aristolochia indica.*
Barberry (Berberidis)	Bark	Decoction and Tincture	Contains the bitter, yellow, crystalline aikaloid berberine.
Berberis (Berberis)	Stem	Tincture	Contains berberine.
Cascarilla (Cascarilla)	Bark	Tincture and Concentrated Infusion	When burnt the bark emits a pleasant aromatic odour.
Condurango (Condurango)	Bark	Wine and Liquid Extract	Contains a glucoside which coagulates when its aqueous solutions are boiled.
Coptis Rhizome (CoptisRhizoma)	Rhizome	—	Contains about 8 per cent. of berberine. Used in China and India.
Coscinium (Coscinium)	Stem	Concentrated Infusion	Used as the equivalent of calumba in India and the Eastern Colonies. Is sometimes imported under the name Ceylon calumba.
Cusparia Bark (Cuspariæ Cortex)	Bark	Concentrated Infusion	Often given together with preparations of cinchona.

TABLE X—VEGETABLE BITTERS OF SECONDARY IMPORTANCE—*continued*

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Remarks*
Hops (Lupulus)	Fruit (strobiles)	Concentrated Infusion and Tincture	Fruits should be fresh and recently dried; when stored, valerianic acid is formed with a consequently unpleasant odour.
Picrorhiza (Picrorhiza)	Rhizome ..	Liquid Extract and Tincture	Indigenous to the Himalayas and used in India as a bitter.
Simaruba Bark (Simarubæ Cortex)	Root Bark	Decoction	Sometimes the Decoction is made with an equal quantity of cinnamon bark.
Tinospora (Tinospora)	Stem ..	Concentrated Infusion and Tincture	Contains the yellow alkaloid berberine. Used in India as a substitute for calumba.
Toddalia (Toddalia)	Root Bark	Concentrated Infusion	Used in India as a substitute for cusparia.

Chapter XV

RUBEFACIENTS AND SKIN REMEDIES

THIS chapter is devoted to a discussion of two small groups of vegetable substances which are mainly employed in preparations for external application. None of the drugs discussed in either group should be regarded as of primary importance since many medicaments in these classes fall outside the scope of this book. Thus, among rubefacients, preparations of volatile oils, and especially of oil of turpentine, are much favoured, while cantharidin, an active principle found in the Spanish fly (*Cantharis vesicatoria*) is probably the most important counter-irritant. Again, inorganic compounds and synthetic disinfectants are almost always more satisfactory for the treatment of skin diseases than drugs of vegetable origin.

RUBEFACIENTS

The practice of applying irritants to the skin in internal diseases is one of great antiquity. The initial effects of such applications are superficial congestion and redness of the part, and those drugs which produce only this degree of irritation in ordinary circumstances are known as *rubefacients*, while stronger substances which cause blistering are called *vesicants* and still more powerful drugs that induce small discrete suppurations are designated *pustulants*. The purpose of treatment by counter-irritation is the relief of pain caused by disorders affecting some internal part of the body. Thus, for example, in cases where the stomach is affected, the application of a rubefacient to the epigastrium will often afford some relief and this phenomenon is generally explained by supposing that the pain of the visceral disease is due to a disorder of the synapses in the spinal cord at the level at which the nerve fibres from the viscus and from the superficial tissues meet, whence it is possible that new impulses reaching this area from the skin may alter its condition or may occupy a common path to the brain to the exclusion of impulses arising from the seat of the disease. Counter-irritants are used in a number of complaints, often without any idea of what precise effects they will elicit, but merely because they have been found to afford relief in similar conditions. As a rule they are placed over the affected organ because it generally happens that the nerve fibres from the internal part and from the immediately superficial tissues meet the cord in close juxtaposition. However, in the head, the segmental arrangement is rendered very irregular by the compression in embryonic development and counter-irritants are often found to be most effective when placed at some distance from the seat of pain as, for example, behind the ear

in certain forms of facial neuralgia. Rubefacients are used in the treatment of acute inflammation of the lungs and pleura, in gastric disorders accompanied by much pain, in colic, in neuralgia and in neuritis. From a consideration of the foregoing it will be appreciated that this group of drugs can only be expected to give a measure of relief to the patient as distinct from effecting actual cure although, by minimising pain, they sometimes assist the curative effect of other remedial measures which are simultaneously applied, or accelerate natural processes of recovery.

CAPSICUM

The official drug consists of the dried ripe fruits of *Capsicum minimum* which occur as dull orange-red, two-celled bodies from 12 to 20 mm. long and up to 7 mm. in greatest width. The drug possesses a faint characteristic odour and an extremely pungent taste. The best material is cultivated in Sierra Leone and Zanzibar. Other species of capsicum are found in commerce; thus Japanese chillies, which are much brighter in colour than the official fruit but also less pungent, are largely used for preparing powdered cayenne pepper which is employed as a condiment, while paprika and bird pepper are severally derived from different species of the same genus.

Chemistry of Capsicum

The pungency of capsicum has been demonstrated to be due to capsaicin which chiefly resides in the dissepiment dividing the two cells of the fruit. The drug also contains fixed oil, red colouring matter and a liquid alkaloid, but none of these is pungent. Capsaicin, which is a crystallisable compound, is present to the extent of about 0·02 per cent., but no satisfactory method of chemical assay has been evolved. An approximate comparison between samples can be obtained by the simple expedient of testing their relative pungency. For this purpose it is convenient to macerate 0·1 gm. of ground capsicum with 100 ml. of alcohol during 24 hours, filter and add the filtrate to a 10 per cent. aqueous solution of sugar in such proportion that a distinct but weak pungency is perceptible to the tongue or throat. A good specimen should respond to this test in a dilution of 1 in 50,000, while the pungency of Japanese chillies may only be just detectable in solution of double this strength. The detection of capsicum present as an adulterant in ginger beverages and galenicals has already been discussed (see page 159).

Pharmacy of Capsicum

For internal use as a stimulant and carminative to the alimentary tract a 1 in 20 tincture in 60 per cent. alcohol is used in association with bitters and tonics. For the principal use of capsicum as an external counter-irritant an ointment is prepared by digesting on a water-bath for 1 hour the bruised drug with yellow soft paraffin to which a proportion

of lard and hard paraffin has been added, straining and stirring until cold; the proportion of drug to basis in this preparation is approximately 1 to 5. Capsicum wool affords a useful method of applying the rubefacient to the chest: it is made by mixing 10 parts of a 2 in 1 alcoholic liquid extract of the powdered drug with 70 parts of alcohol and pouring the solution over the cotton under pressure so that the latter becomes evenly saturated with the liquid; after drying, the medicated wool is stored in cartons. Since the original pale orange colour of the fresh preparation tends to fade during storage it is advisable to employ cotton-wool which has first been dyed with eosin.

For the application of counter-irritants the various plasters constitute important pharmaceutical preparations. Rubber capsicum plaster is prepared by evaporating 10 parts of a 2 in 1 liquid extract to half its weight and mixing with 95 parts of rubber adhesive plaster. The latter is prepared by first macerating 20·3 parts of masticated indiarubber with six times its weight of mineral naphtha until a homogeneous jelly is obtained, then melting together 53 parts of wool fat and 6·25 parts of copaiba, heating the mixture to 100° C. for 10 minutes, allowing to partially cool, stirring in half its weight of mineral naphtha and adding 20·3 parts of powdered and dried orris root, 0·4 part of thymol and 0·6 part of methyl salicylate and, when the mixture has cooled, mixing in the indiarubber solution. The preparation is then completed by straining through a double layer of muslin.

Another variety of capsicum plaster is made by evaporating the alcohol from 10 parts of the 2 in 1 liquid extract, then adding the residue to 100 parts of melted plaster of colophony. The latter, which is also known as resin plaster, is made by melting together 10 parts of colophony and 85 parts of plaster of lead and incorporating a small proportion of hard soap. Lead plaster or, as it is sometimes termed, diachylon plaster, in its turn is made by saponifying 2 parts of olive oil with 1 part of lead monoxide in the presence of boiling water, removing the resulting mass from the cooled mixture, kneading it with hot water and removing the excess of the latter by manipulation. It is generally convenient to spread these various forms of plaster masses on some supporting material such as calico, felt or thin leather before applying the medicament to the skin of the patient. Finally, it may be observed that capsicum finds a place in many proprietary liniments intended for the treatment of rheumatism and neuralgia.

MUSTARD (SINAPIS)

There are two varieties of this drug which are known as white mustard, the dried ripe seeds of *Brassica alba*, and black mustard, consisting of the seeds of *Brassica sinapioides*, both plants being annual herbs largely

cultivated in temperate climates. The seeds of the white kind are actually yellow in colour, minutely pitted, nearly spherical and about 2 mm. in diameter, while the dark reddish-brown or greyish-brown seeds of the " black " species are approximately 1 mm. in diameter and exhibit a pitted outer surface.

Chemistry of Mustard

The white seeds contain a crystalline glucoside, sinalbin, together with an enzyme, myrosin, which in the presence of water hydrolyses the glucoside producing acrinyl isothiocyanate, sinapine acid sulphate and dextrose. Acrinyl isothiocyanate is a *non-volatile*, yellow, oily liquid with a pungent taste and possesses a powerful rubefacient action. In contrast, the black seeds contain a crystalline glucoside, sinigrin, together with the enzyme, myrosin, which in the presence of water hydrolyses the glucoside producing allyl isothiocyanate, potassium acid sulphate and dextrose. Allyl isothiocyanate is a *volatile*, mobile liquid with an extremely pungent odour and taste and is employed in medicine under the name of volatile oil of mustard (Oleum Sinapis Volatile). Allyl isothiocyanate is quite easily distilled from the seeds and, as the oil is more convenient in use than the crude drug, it follows that, pharmaceutically, the black variety is the more important. In addition to the constituents mentioned above both kinds contain 25 per cent. or more of fixed oil which has a mild rubefacient action.

Determination of Allyl Isothiocyanate in Black Mustard

The yield of allyl isothiocyanate from the powdered seed may be effected by the following procedure :—

A suitable quantity of the sample, usually 5 gm., is transferred to a distillation flask, 100 ml. of water and 20 ml. of 90 per cent. alcohol added, the vessel closed and the contents maintained at a temperature of 30° to 35° C. for 6 hours. The flask is then attached to a condenser and the contents slowly distilled over a glycerin bath, the delivery tube of the condenser being arranged to dip into 10 ml. of dilute ammonia contained in a 100 ml. graduated flask. When about 50 ml. of distillate has been collected 20 ml. of decinormal silver nitrate is added and the distillation is continued until the receiver is filled to the mark. The mixture is transferred to a suitable container attached to a refluxing condenser, gently boiled for 30 minutes, allowed to cool, the volume adjusted if necessary to exactly 100 ml. with water, the mixture filtered, in order to remove the insoluble silver sulphide which has been produced, and the excess of silver nitrate in 50 ml. of the filtrate titrated with decinormal ammonium thiocyanate using ferric ammonium sulphate as indicator. The result is calculated on the basis that 1 ml. of decinormal silver nitrate

is equivalent to 0·004956 gm. of allyl isothiocyanate yielded by the quantity of drug taken for assay which, in this instance, will be half the amount originally weighed out.

Pharmacy of Mustard

A mixture of equal proportions of powdered black and white mustard is used as a counter-irritant either in the form of poultice (Cataplasma Sinapis) or as mustard paper. The former is prepared by adding 28 parts of crushed linseed to about 70 parts of boiling water, then adding 2 parts of powdered mustard previously rubbed into a smooth paste with a little tepid water ; it is mainly employed for the alleviation of pleurisy and bronchitis. To make mustard paper (Charta Sinapis, British Pharmacopœia 1898) the fixed oil is removed from a mixture of equal proportions of the two species of bruised seeds by percolation with benzene, the dried fat-free drug reduced to No. 60 powder and 5 gm. mixed with 18 ml. of indiarubber solution and spread by means of a brush on one side of a piece of cartridge paper. The dried preparation is used as a counter-irritant for the treatment of lumbago, congestion of the lungs and bronchitis. A mixture of white and black mustard gives the best results as the former contains an excess of ferment and the latter of glucoside. The drug is more generally employed in medicine as the volatile oil compounded as liniment of mustard, which consists of an alcoholic solution containing 5·5 per cent. of camphor, 12·5 per cent. of castor oil and 3·5 per cent. of volatile oil of mustard.

MEZEREON BARK (MEZEREI CORTEX)

This is obtained from various species of *Daphne* such as *D. Mezereum* and *D. Gnidium* (N.O. Thymelaceæ), shrubs which flourish in Southern Europe and Algeria, while the bark of the British spurge-laurel (*D. laureola*) may also be employed. It occurs in long, thin, quilled, fibrous strips from 0·5 to 2 cm. wide from which the paper-like cork easily separates. The drug is almost odourless but possesses a persistent, burning taste. The active principle is a greenish-brown, acrid resin called mezerein ; in addition, the bark contains a glucoside and fixed oil. The vesicant property of this drug can be demonstrated by moistening it with vinegar and applying to the skin when blistering will occur in the course of a few hours or days. An ethereal extract is included as an ingredient of compound liniment of mustard which consists essentially of an alcoholic solution containing, besides the mezereon, volatile oil of mustard, camphor and castor oil. Mezereon is now only of minor importance but it is still utilised as an ingredient of concentrated compound solution of sarsaparilla (see page 109), which is a useful vehicle for the administration of potassium iodide.

EUPHORBIUM

Euphorbium is a resin obtained by incision of the stem of *Euphorbia resinifera* (N.O. Euphorbiaceæ), which is found in the mountainous districts of Morocco. The milky latex which exudes from the incised stems hardens on exposure to air and forms resinous pieces which occur in commerce as dull yellow or brown tears or irregular masses often mixed with pieces of stem. The resin contains about 40 per cent. of a colourless, tasteless, odourless crystalline substance termed euphorbone together with euphorbo-resene, euphorbic acid, calcium malate and an intensely acrid water-soluble substance, the true nature of which has not been elucidated.

It is said that this drug was discovered by Juba II, King of Mauretania (approximately the modern Morocco), who named it after his chief physician, Euphorbus. Juba, who died about the year 20 B.C., took considerable interest in medicine, and wrote books on materia medica and physiology. Taken internally, euphorbium is emetic and powerfully cathartic, but on account of its violent action its use for these purposes has been abandoned. It is now only employed as a vesicant in veterinary practice. Care is necessary when handling the powdered drug, since not only does it cause severe inflammation of the nasal mucous membrane but, if imbibed, it may set up acute nephritis. It is interesting to note that the majority of some 2500 species of plants belonging to the Natural Order Euphorbiaceæ agree in being furnished with a juice, often milky, which is highly acrid, poisonous, and sometimes corrosive. A familiar example in Britain is the common garden weed, petty spurge (*Euphorbia peplus*); if the white latex which exudes when the stem of this plant is broken be allowed to touch the tongue the latter is rendered sore for hours afterwards. The juice of an allied species (*E. hibernus*) is used by salmon poachers in Ireland in order to poison the fish, which it is said to do throughout long reaches of the rivers. It has been alleged that the manchineel tree of the tropics, which also belongs to this Natural Order, is so poisonous that persons have died merely as a result of sleeping beneath its shade. More useful to mankind is the india-rubber tree, *Hevea brasiliensis*, indigenous to Brazil but now largely cultivated in the Federated Malay States, Ceylon and elsewhere. The milky white latex so copiously secreted by this plant is collected, preserved by the addition of ammonia, shipped to Europe or the United States and then vulcanised by treatment with sulphur to produce the rubber with which we are all familiar.

BURGUNDY PITCH

This consists of a resinous exudation obtained from the stem of a coniferous tree *Picea excelsa*, the crude material being purified by melting under water and straining. It occurs as an opaque, hard, brittle, reddish

or yellowish-brown substance which breaks with a conchoidal fracture. When stored for some time it gradually flows to the contour of the vessel in which it is contained. It is employed for the preparation of pitch plaster (Emplastrum Picis, British Pharmacopœia 1898), which is made by melting together 52 parts of Burgundy pitch, 26 parts of olibanum (frankincense), 9 parts each of colophony and yellow beeswax, adding 4 parts each of olive oil and water and, while constantly stirring, evaporating to a suitable consistency. Pitch plaster, which is also known by the quaint synonym "Poor Man's Plaster," is a mild counter-irritant and is applied to the chest for the treatment of bronchitis and is also used for the relief of pain in rheumatism and lumbago.

SKIN REMEDIES

The majority of medicaments used for the treatment of skin diseases take the form of inorganic chemicals or synthetic coal-tar derivatives, but a few drugs of purely vegetable origin still retain a position of some importance, particularly for the treatment of certain complaints of parasitic origin. Some of these drugs have been known and used for centuries as, for example, stavesacre and balsam of Peru, while rotenone, the active resinous principle of derris root, has been applied medicinally only during the last few years.

ARAROBA (CRUDE CHRYSAROBIN)

Araroba, or goa powder, is a substance scraped from the cavities of the trunk of a large tree (*Andira Araroba*) which grows in the damp forests of Bahia, Brazil. It is exported in a moist condition, containing woody debris, as an umber-brown powder and is partially purified by treating with boiling solution of potassium hydroxide, filtering and reprecipitating from the filtrate by acidifying with hydrochloric acid. The drug occurs as a brownish-yellow to dark brown powder, which should yield not less than 50 per cent. to hot benzene, while as much as 75 per cent. is sometimes obtained. The material soluble in benzene is termed chrysarobin and is the portion generally employed in medicine, although in India araroba itself is sometimes preferred. It is usually administered as an ointment, prepared by treating the drug with an equal weight of glacial acetic acid and incorporating 1 part of the mixture into 7 parts of lard.

CHRYSAROBIN

An odourless, tasteless, light, microcrystalline, yellowish powder obtained, as already indicated, by extracting araroba with hot benzene, evaporating the solution and powdering the residue. It contains

chrysophanolanthranol (the monomethyl ether of dehydroemodinanthranol), chrysophanol (chrysophanic acid), emodin monomethyl ether and ararobinol. When heated it melts and evolves yellow fumes. It is slightly soluble in alcohol, almost insoluble in water, but completely dissolved by hot chloroform or hot benzene. It is an excellent remedy for tinea (ringworm) and is frequently employed for the alleviation of psoriasis and alopecia and for these purposes is usually employed as an ointment containing 4 per cent. of medicament in a paraffin basis. Chrysarobin is toxic when absorbed and for this reason the ointment should not be spread over too large an area of the skin. A useful preparation incorporating this drug is chrysarobin paint (Pigmentum Chrysarobini) made by dissolving 1 part in solution of gutta percha and making up to 10 parts with the same solvent. The latter is prepared by adding 10 parts of gutta percha, in thin slices, to 60 parts of chloroform, shaking frequently until solution is effected, adding 10 parts of lead carbonate previously mixed with 30 parts of chloroform, shaking, setting aside until insoluble matter has subsided, and decanting.

BALSAM OF PERU

This material is a dark brown, viscid, non-glutinous liquid, having an agreeable vanilla-like odour, which originates from *Myroxylon Pereirœ*, a tree about 50 feet high, which grows in the forests of San Salvador, in Central America. The balsam is not a normal exudation, but its secretion is induced by first beating the bark and, about three days later, scorching it with burning faggots. When, after a few more days, the balsam exudes, it is soaked up by rags applied to the wounded places, then recovered from the pieces of cloth by immersing them in vats of hot water, whence the immiscible balsam separates at the bottom.

Balsam of Peru contains at least 53 per cent. of an oily ester, known as " cinnamein " and consisting almost entirely of benzyl cinnamate, while the remainder of the drug is largely resinous matter. Factitious products, prepared from synthetic benzyl cinnamate and cheap resinous material, sometimes appear on the market and a number of colour reactions have been proposed to distinguish the genuine material from the artificial, but most of them are of doubtful value.

Determination of Benzyl Cinnamate in Balsam of Peru

A weighed quantity of the sample, about 1 gm., is dissolved in ether, the solution transferred to a separating funnel and extracted with two or three portions of dilute aqueous solution of sodium hydroxide. The alkaline extracts are separated, mixed, shaken with ether and the latter, after separation, added to the original ethereal solution, the aqueous alkali being rejected. The ether, which now contains the benzyl cinnamate freed from resinous material, is washed with a little water, separated

and transferred to a tared flask ; the solvent is removed by distillation, the residue treated with a little absolute alcohol, the latter evaporated, the residual ester dried at 100° C. and weighed. When this benzyl cinnamate is saponified by boiling with a known quantity of standard alcoholic potassium hydroxide solution and the excess of the latter determined by titration with standard acid, the indicated ester value (mg. of potassium hydroxide required by 1 gm. of ester to effect the saponification) should not be less than 235, the theoretical value for benzyl cinnamate being 235·5.

Pharmacy of Balsam of Peru

The balsam is sometimes employed in the pure state, or mixed with an equal quantity of castor oil, for the treatment of skin affections Alternatively, it may be administered as a 1 in 8 ointment made with a basis of prepared lard. Balsam of Peru collodion prepared by mixing 10 parts of balsam with 30 parts of acetone and adding sufficient acetone collodion to produce 100 parts is another useful preparation for the treatment of certain skin diseases. Acetone collodion is made by dissolving 5 parts of pyroxylin (cellulose tetranitrate) in 50 parts of acetone, adding to the solution 2 parts of oil of cloves, 25 parts of amyl acetate, 20 parts of benzene and diluting to 100 parts with more acetone.

DERRIS

The rhizome and roots of *Derris elliptica* and *D. malaccensis*, leguminous climbing plants indigenous to Malay and the East Indies, contain up to about 8 per cent. of a substance termed rotenone ($C_{23}H_{22}O_6$) which is extremely poisonous to cold-blooded organisms such as insects and fish and, in recent years, it has been successfully applied to the treatment of scabies, the parasite responsible for this disease being effectively destroyed. The root itself, which is also known as tuba root, is extensively used as a powder emulsified with soap and water to protect cattle against the warble fly which burrows in the skin and ruins the hide. For medicinal purposes the rotenone is isolated and applied to the skin in the form of an emulsion. Derris is only one of a number of plants containing rotenone, others being black and white haiari (a species of *Lonchocarpus*, from Guiana), cubé root (*Lonchocarpus nicou* and other species, from South America), barbasco root and Brazilian timbo root. Many of these are used by the natives for poisoning streams in order to kill the fish.

In addition to rotenone, derris contains other active substances of which deguelin has a toxicity to insects about one-tenth that of rotenone, In addition, the drug contains varying proportions of resinous material and the ether-soluble matter varies from about 7 to 25 per cent.

Determination of Rotenone in Derris

Several methods have been proposed for assessing the value of consignments of this drug, but none is entirely satisfactory and the procedures are subject to constant modification by investigators. The simplest method, and perhaps the most useful, depends upon extraction of the powdered root with hot carbon tetrachloride and subsequent crystallisation from this solvent by cooling.

A weighed quantity, say 25 gm., of the powdered root is extracted for at least 12 hours with carbon tetrachloride using a continuous extraction apparatus. The resulting solution is transferred to a 50-ml. beaker, concentrated by evaporation on a water-bath until the volume approximates to 15 ml. and then allowed to cool. If no sign of crystallisation is apparent then it is necessary to " seed " the liquid by stirring with a glass rod, which has been dipped in the crystals obtained from a previous determination and has a little of the crystalline dust adhering to it. The mixture is allowed to stand overnight to permit complete separation of the crystals, then the beaker is immersed in a mixture of crushed ice and water for 10 minutes. The rotenone is now transferred to a tared sintered glass crucible, the flask being washed with not more than 5 ml. of carbon tetrachloride previously cooled to 0° C.; the crucible and the contained crystals are then allowed to dry to constant weight at room temperature. The compound thus isolated is rotenone containing "carbon tetrachloride of crystallisation" and it is therefore necessary to multiply the weight found by the factor 0·719 in order to derive the amount of rotenone isolated from the drug taken for assay.

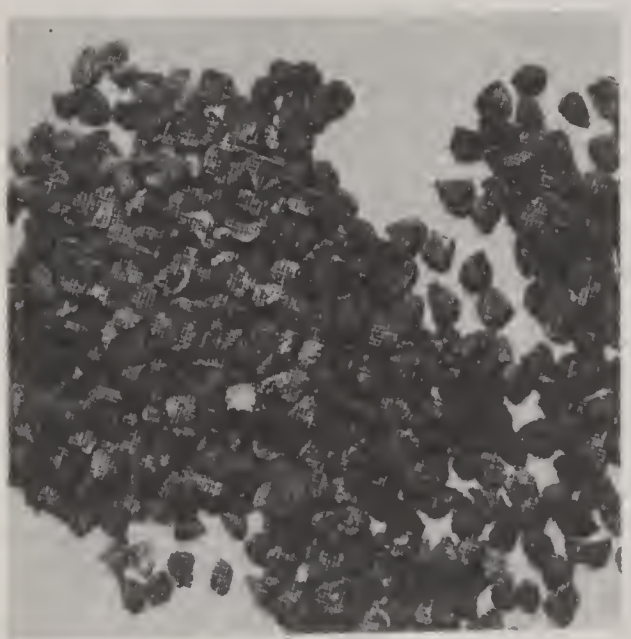


Fig. 1.—STAVESACRE SEEDS

Preparations of these poisonous seeds are employed for the destruction of lice. Their use has considerably declined since the introduction of modern coal-tar disinfectants and generally improved hygienic conditions.

STAVESACRE (STAPHISAGRIÆ SEMINA)

By contrast with the very recent therapeutic application of derris, preparations made from the seeds of *Delphinium Staphisagria*, a herb indigenous to Asia Minor and Southern Europe, were extensively employed by the ancients for the destruction of head lice and their ova. The odourless seeds are obscurely quadrangular or triangular in shape and measure approximately

6 mm. in length, while the outer coat is characterised by a reticulated and pitted surface. The drug contains several alkaloids, amounting altogether to about 1 per cent. Of these, the most important are delphinine, $C_{31}H_{49}O_7N$, delphisine and delphinoidine. The first two are intensely toxic. The drug may be applied as an ointment, made by digesting the crushed seeds with benzoinated lard on a water-bath and stiffening the resulting preparation by the addition of beeswax. Stavesacre lotion is prepared by treating the powdered seeds with boiling dilute acetic acid and, after allowing to cool, adding a dilute alcoholic solution of the oils of geranium, lavender and lemon, and finally diluting with glycerin and water. The use of this drug has now largely given place to modern and less dangerous methods for destroying pediculi.

OTHER SKIN REMEDIES AND PARASITICIDES

A few other drugs of vegetable origin which are used in limited degree for the treatment of skin diseases or as parasiticides call for brief mention.

PYRETHRUM FLOWERS, which consist of the dried flower-heads of *Chrysanthemum cinerariæfolium* and certain other species, have long been used as an insecticide, but, more recently, the extract obtained by treatment of the drug with petroleum ether has been effectively used in the form of an ointment for the treatment of scabies. The herb is indigenous to Dalmatia and is cultivated there as well as in Japan and Kenya. It contains two active principles termed pyrethrin I and pyrethrin II, which are the esters of a keto-alcohol called pyrethrolone and chrysanthemum monocarboxylic and dicarboxylic acids respectively. Pyrethrum is harmless to human beings and domestic animals and because of its value as an insecticide it has been the subject of considerable investigation in recent years.

ELEMI is an oleo-resin exported from Manila which occurs in commerce as a crystalline, honey-like mass with a fragrant odour and pungent bitter taste. The British Pharmacopœia 1885 included an ointment of elemi made by melting together 1 part of the oleo-resin with 4 parts of simple ointment, filtering through flannel and stirring until the mixture solidified : the official simple ointment of that time comprised a mixture of 2 parts of white beeswax, 3 parts of benzoated lard (now called benzoinated lard) and 3 parts by volume of almond oil. This preparation was employed as a local stimulant to ulcers and chronic skin diseases, its properties being similar to those of turpentine in which it is sometimes ordered to be dissolved before mixing with the ointment base.

WHITE HELLEBORE (VERATRI ALBI RHIZOMA) is the rhizome of a herbaceous plant (*Veratrum album*) growing in Central and Southern Europe and containing resins and about 1 per cent. of highly toxic alkaloidal material. It has been used as a parasiticide in scabies but is now rarely employed in medicine.

STOCKHOLM TAR (PIX LIQUIDA) is obtained by the destructive distillation of pine wood and contains a complex mixture of phenols and hydrocarbons. Tar ointment (Unguentum Picis Liquidæ), which contains 70 per cent. of the drug in a basis of yellow beeswax and lard, is used for the treatment of skin complaints. The value of wood tar in this connection is rather doubtful and it is probably more useful as an ingredient of cough and bronchitis mixtures.

SABADILLA (CEVADILLA), the dried ripe seeds of *Schœnocaulon officinale*, a liliaceous plant growing on the low mountain slopes of Mexico, Guatemala and Venezuela, is chiefly employed as a source of the mixture of alkaloids termed veratrine. This, which is extremely toxic, has been employed as the oleate in a basis of lard as an anodyne in facial neuralgia, while a vinegar of sabadilla can be used for the destruction of head lice.

COCCULUS INDICUS, OR LEVANT NUT, the fruit of *Anamirta paniculata*, a climbing shrub indigenous to Eastern India and the Malay Archipelago, is principally interesting as the source of the powerful poison picrotoxin. The fruit is brownish-black in colour, about 12 mm. in length and approximately reniform in shape. The powdered drug has been used in the form of an ointment for destroying pediculi.

Chapter XVI

CYANOGENETIC DRUGS

IN Chapter I allusion was made to the glucosidal substance present in bitter almonds known as amygdalin, which decomposes into benzaldehyde, dextrose and hydrocyanic acid under the influence of the enzyme emulsin. In small doses hydrocyanic acid (or prussic acid) is a valuable sedative for the treatment of coughs and digestive disorders, and a small group of vegetable drugs containing this type of glucoside owe their therapeutic virtue to the hydrocyanic acid produced during compounding and are, therefore, conveniently classified as the cyanogenetic drugs.

WILD CHERRY BARK

This, the most important of the cyanogenetic group, is derived from the wild, or black, cherry, *Prunus serotina*, a tree widely distributed over North America, especially throughout the northern and central States. It is official in the British Pharmacopœia 1932, under the name Prunus Serotina, but in the edition of 1914 it was known as Pruni Virginianæ Cortex in allusion to the State of Virginia. The bark usually occurs in flattened, curved or recurved pieces, attaining 12 cm. in length and 5 cm. in width, but generally smaller, and frequently covered with a thin, smooth, glossy, reddish-brown cork interrupted by tangentially elongated whitish lenticels. The commercial drug is often deprived of its cork and may then exhibit either the smooth greenish-brown cortex or the rough-surfaced brown bast as its outer layer. The medicinally important constituent of the bark is mandelonitrile glucoside, or prunasin, a substance analogous to amygdalin and yielding dextrose, benzaldehyde

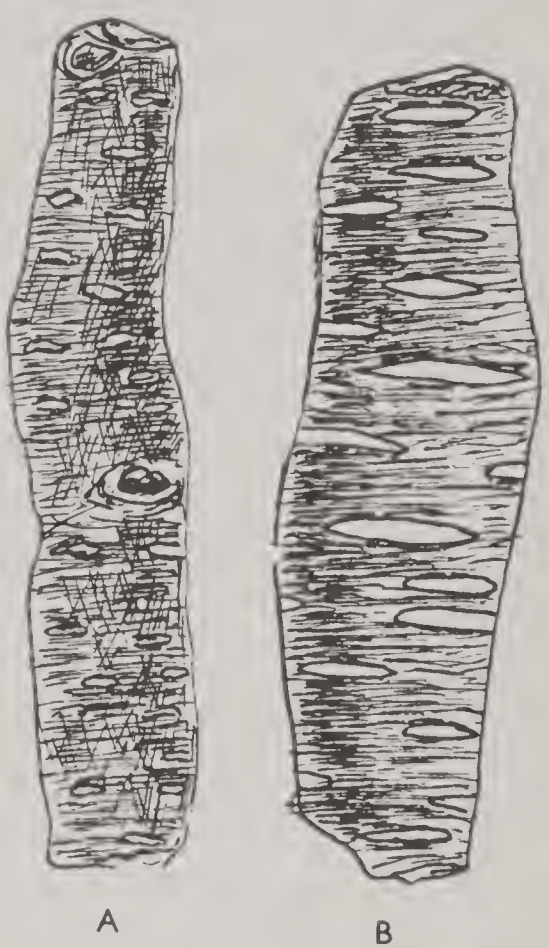


Fig. 1.—WILD CHERRY BARK

The piece at A is young bark showing cork with transverse lenticels, while old bark with scars corresponding to lenticels is shown at B.

and hydrocyanic acid when treated with water and the enzyme ferment; the latter, although present in the drug, is normally segregated in cells separate from those which contain the glucoside.

Chemical Evaluation

Some idea of the relative value of different consignments of the drug may be obtained by determining the proportion of hydrocyanic acid yielded on treatment with water. To effect this, 10 gm. of the powdered sample is introduced into a litre flask, about 100 ml. of water added, the flask being connected on the one side to a condenser fitted with an adapter dipping into a little dilute solution of ammonia and on the other to a steam generator (see Fig. 2). After allowing the drug to macerate for some hours, steam is passed through the suspension for about half an

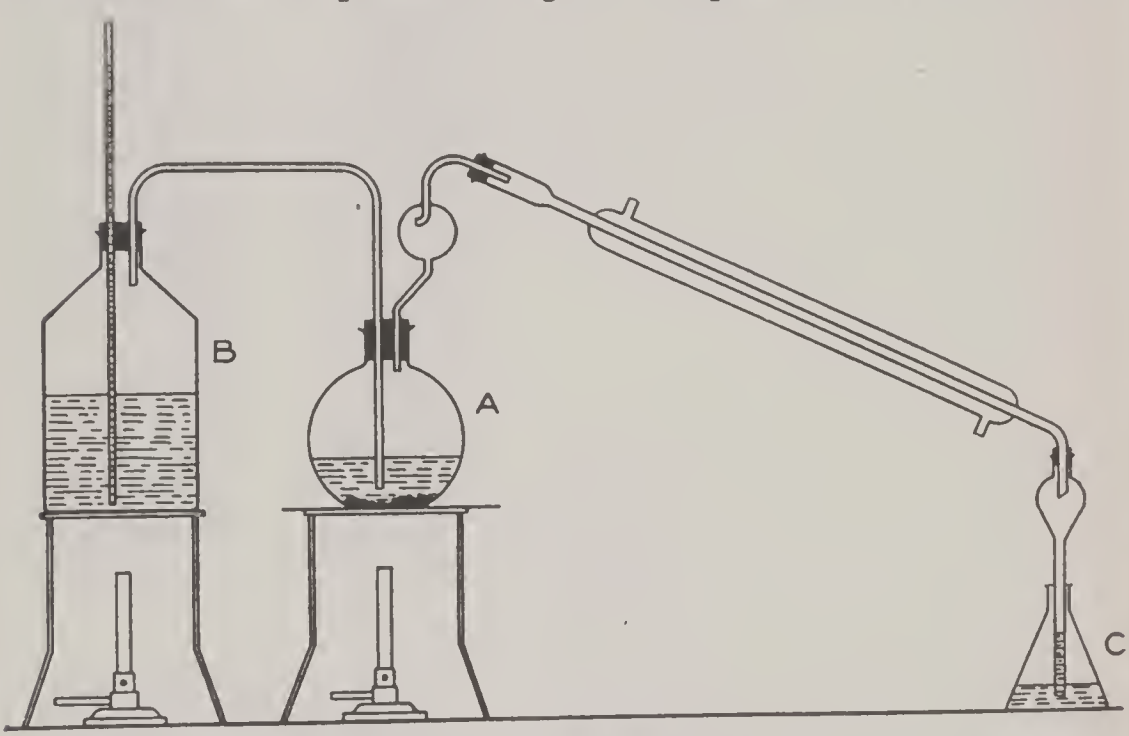


Fig. 2.—DETERMINATION OF AVAILABLE HYDROCYANIC ACID IN WILD CHERRY BARK

The powdered sample is macerated with water in the flask A, then steam, derived from B, is blown through the mixture and the liberated hydrocyanic acid collected in the solution of ammonia contained in C. The resulting solution of cyanide is then titrated with standard silver nitrate, using potassium iodide as indicator.

hour or until all the hydrocyanic acid has distilled over into the dilute ammonia. A few drops of potassium iodide solution are then added to the distillate and the latter titrated with decinormal silver nitrate until a permanent precipitate of silver iodide is just produced. The result is calculated on the basis that 1 ml. of decinormal silver nitrate is equivalent to 0·0054 gm. of hydrocyanic acid yielded by the quantity of drug taken for assay.

It has been shown that the bark of the root contains the largest proportion of the glucoside yielding hydrocyanic acid, the bark of young trees more than that of old ones, while the concentration in the bark of the twigs is generally higher than in the bark of the trunk. The yield of hydrocyanic acid may be expected to vary from 0·08 per cent. for material derived from the trunk to about 0·25 per cent. for freshly gathered root bark.

Pharmacy

The most important preparation of wild cherry bark is the syrup which is included in the Pharmacopœia where it is called Syrupus Pruni Serotinæ, the name having been altered from the former official designation of Syrupus Pruni Virginianæ, while at the same time slight alterations were made in the formula. It is prepared by moistening the powdered bark with a mixture of glycerin and water, setting aside in a closed vessel for 24 hours, then percolating, first with the same mixture, then with distilled water, and collecting the percolate in a vessel containing a prescribed quantity of sucrose. When the combined volume of the percolate and sugar amounts to half that of the final preparation the mixture is agitated until the sucrose has dissolved and the solution is then diluted with more water so that 2000 ml. of syrup is produced from 150 gm. of bark.

This syrup, which contains 40 per cent. of sugar, is excellent as a basic ingredient for cough mixtures. Effective medicines can be compounded by adding appropriate quantities of such preparations as syrup of tolu and camphor water together with expectorant drugs, of which tincture of ipecacuanha and vinegar of squill are the most suitable.

CHERRY-LAUREL LEAVES (LAUROCERASI FOLIA)

Cherry-laurel leaves are obtained from *Prunus Laurocerasus*, an evergreen shrub indigenous to Persia and Asia Minor but cultivated in temperate regions. The leaves, which are used in the fresh state, vary from 12 to 17 cm. in length and from 4 to 5 cm. in breadth ; the upper surface is dark green and glossy while the colour of the under side is paler and exhibits a prominent midrib. The important constituent is the glucoside prulaurasin which resides in the parenchymatous tissue of the leaf, while the endodermis of the midrib and veins contains the enzyme prunase. When the respective cells containing these constituents are ruptured, the prulaurasin is decomposed by contact with the prunase and dextrose, benzaldehyde and hydrocyanic acid are produced.

Pharmacy

Cherry-laurel water (Aqua Laurocerasi) is the only preparation of the drug that is employed for medicinal purposes. It is made by adding 80

parts of the crushed leaves to 250 parts of water contained in a retort, distilling 100 parts of liquid, filtering and adjusting the strength, if necessary, either by adding diluted hydrocyanic acid, or by diluting with water, so that it shall contain 0·1 per cent. by weight of real hydrocyanic acid. The assay of the water which distils over is conducted by titrating with standard silver nitrate, using potassium iodide as indicator, in the manner already described for titrating the distillate in the evaluation of wild cherry bark.

This preparation is employed as a mild sedative for the alleviation of coughs, particularly in association with demulcents such as mucilage of acacia and syrup of orange flowers. It is also employed in conjunction with boric acid in eye lotions (collyria) designed to relieve the irritation arising from severe inflammations.

BITTER ALMOND (AMYGDALA AMARA)

Almond trees, both the sweet and bitter varieties, are widely cultivated in the countries that border on the Mediterranean Sea. As the fruit ripens it splits open, disclosing the hard endocarp, within which the seed is to be found. Bitter almonds are shorter and broader than the ordinary Jordan sweet almond and are distinguished by the odour of benzaldehyde and hydrocyanic acid which is evolved when they are triturated with water, as well as by their bitter taste. The principal constituents are the fixed oil, the glucoside amygdalin and the enzyme emulsin. If the cake remaining after the expression of the fixed oil is mixed with warm water, macerated for some time, and the mash thus formed submitted to steam distillation, hydrocyanic acid and benzaldehyde distil over, partly in the free state but mainly in unstable combination as benzaldehyde-cyanhydrin ; the distillate, freed from cyanide, forms essential oil of almonds which, unlike the majority of volatile oils, is heavier than water.

Pharmacy

A bitter almond mixture, used as a basis for skin lotions, is prepared by blanching the seeds and triturating with distilled water to form a thin paste, then gradually adding more water until a preparation containing 7·5 parts by weight of almonds in 100 parts by volume of liquid is produced. More important is the compound bitter almond powder made by drying freshly blanched almonds, reducing them to a smooth pasty consistency in a mortar, adding half their weight of powdered gum acacia and triturating until a uniform preparation is produced. From this powder a compound bitter almond mixture is made by mixing 12·5 parts by weight with water, diluting to 100 parts by volume and straining ; this contains a small proportion of hydrocyanic acid and is employed as a remedy for coughs.

ELDER LEAVES (SAMBUCI FOLIA)

The Rev. C. A. Johns in his book "The Flowers of the Field" quotes John Evelyn, the seventeenth-century diarist, as having written of the elder tree: "If the medicinal properties of the leaves, bark, berries, etc., were thoroughly known, I cannot tell what our countryman could ail for which he could not find a remedy from every hedge, either for sickness or wound." This judgment has not withstood the test of modern scientific inquiry, for the elder is now rarely used in pharmacy. The leaves and bark contain an alkaloid called sambucine, a purgative resin and the cyanogenetic glucoside sambunigrin, which is isomeric, but not identical, with the corresponding substance occurring in wild cherry bark already referred to as prunasin.

The Dublin Pharmacopœia for 1826 contained a specification for a green elder ointment made by heating the fresh leaves with lard and suet until the colour is extracted, then filtering through cloth. It is stated to serve as a remedy for sprains, bruises and chilblains, presumably any beneficial action it may possess being due to the sedative action of hydrocyanic acid on the peripheral nerve endings.

In conclusion, it may be remarked that elder flowers are employed to a small extent for the preparation of elder-flower water (Aqua Sambuci) which is occasionally used as a basis for lotions. The most important constituent of elder flowers is a trace of volatile oil; the cyanogenetic principle, characteristic of the leaf and bark, is absent.

Chapter XVII

EXPECTORANTS, ETC.

EXPECTORANTS are drugs which assist in the treatment of inflammatory conditions of the respiratory tract. They increase the secretion of the bronchial mucous membrane and at the same time render it less viscid so that the mucus can be coughed up more easily. The additional secretion may also be of service by protecting the inflamed and irritable membrane from cold air and thereby helping to alleviate the cough. The most important vegetable drugs belonging to this class, namely, ipecacuanha, senega, squill and quillaia, have already been discussed in earlier chapters of this book, but, apart from these, there remain the three balsams, benzoin, tolu and storax, which are widely used, and, in addition, a group of oleo-gum-resins, as well as a few vegetable products of minor importance, some of which are, nevertheless, often met with in pharmaceutical practice.

Fig. 1.—AN ORIGINAL CASE OF BENZOIN, SHOWING THE BALSAM IN ONE SOLID BLOCK

The balsam is introduced into the case in a semi-solid condition, and hardens and becomes brittle during transit.

BENZOIN

This balsam is derived from *Styrax Benzoin*, a tree indigenous to Sumatra, Siam (Thailand) and Java, and most of the material selected for pharmaceutical use comes from the first-named country. The secretion of benzoin does not occur under normal conditions and it is necessary to hack the trunk of the tree with an axe, making an incision sufficiently deep to injure the cambium layer, in order to induce an exudation of benzoin. When first produced the balsam is liquid, but it soon becomes viscous, when it is collected and

packed in cases ready for the market. In the course of a few weeks it becomes quite hard and brittle and consists of whitish or reddish tears embedded in a greyish-brown or reddish-brown translucent matrix. The material possesses an agreeable aromatic odour.

Chemistry of Benzoin

The dry alcohol-soluble portion of benzoin contains between 30 and 60 per cent. of total balsamic acids consisting of a mixture of free

Fig. 2.—An original block of Sumatra benzoin removed from the case and broken to show the structure and the numerous embedded white tears

Fig. 3.—Determination of alcohol-insoluble matter in benzoin by extraction of the soluble matter with alcohol in a Soxhlet apparatus

benzoic and free cinnamic acids which together amount to between 19 and 29 per cent. while the remainder is combined in the form of various esters. In addition to resinous material, there may be present up to 20 per cent. of woody debris which is insoluble in 90 per cent. alcohol.

Analysis of Benzoin

Consignments of this balsam are liable to differ considerably in composition whence its analytical control becomes a question of some importance. A test for the identity of Sumatra benzoin consists in

Fig. 4.—Determination of total balsamic acids in benzoin

Distributing the syrupy liquid over the inner surface of the flask to facilitate drying.

heating a little with a solution of potassium permanganate, when a faint odour of benzaldehyde should be produced, thus indicating the presence of cinnamic acid which is not usually found in Siam benzoin. The moisture content, which should not exceed 10 per cent., is determined by drying *in vacuo* over sulphuric acid. The proportion insoluble in 90 per cent. alcohol is determined by extracting a powdered sample representative of the bulk using a continuous extraction apparatus either of the Soxhlet type (Fig. 3, see also page 124), or an apparatus similar to that employed in the assay of cinchona (see page 44). When all the soluble matter has been dissolved out, the thimble is removed from the apparatus, the contents dried, and the amount of insoluble woody debris weighed. The determination of the total balsamic acids and the free balsamic acids is a particularly interesting procedure and was originated by T. Tusting Cocking.

Determination of Total Balsamic Acids

To the alcoholic solution obtained in the determination of the insoluble matter is added a slight excess of alcoholic potassium hydroxide and the mixture is boiled under a reflux condenser to saponify the esters, after which the bulk of the alcohol is evaporated and the saponified mass is dissolved in hot water. To this is added a solution of magnesium sulphate which reacts with the potassium salts of the balsamic acids and resin acids, produced during the saponification, forming water-soluble magnesium salts of the balsamic acids and precipitating water-insoluble salts of the resin acids, while the excess of magnesium sulphate used is precipitated as magnesium hydroxide by the excess of potassium hydroxide present.

The mixture is now filtered on a Büchner funnel (using suction) and the residual magma washed with a little water and discarded. The filtrate, containing the balsamic acids as magnesium salts, is transferred to a separating funnel, acidified with hydrochloric acid and the liberated balsamic acids are extracted by shaking with several portions of ether. The ether also extracts small quantities of non-acid substances and, in order to separate the acids from the non-acids, it is necessary to shake the ethereal solution with several portions of an aqueous solution of

sodium bicarbonate which reacts with the balsamic acids forming water-soluble sodium salts, but leaves the non-acids behind in the ether. The aqueous solutions are then acidified with hydrochloric acid and the balsamic acids again extracted with ether, this time in a state approaching purity. The ethereal solution is evaporated to low bulk and the last portion of ether is allowed to evaporate spontaneously while the flask containing the residue is rotated so as to distribute the syrupy liquid over the surface. As the last traces of ether evaporate, the transparent pale brown gummy residue, consisting of a mixture of benzoic and cinnamic acids, begins to crystallise and in a few minutes becomes a white mass of minute crystals (see Figs. 4 and 5). The residue cannot be dried by heat since the balsamic acids are volatile ; it is therefore dried in a vacuum desiccator over sulphuric acid and finally weighed.

Determination of Free Balsamic Acids

The alcoholic solution from a duplicate determination of the alcohol-insoluble matter is evaporated until it measures about 17 ml. and to this hot solution is added rapidly 60 ml. of water containing in solution 0·5 gm. of potassium hydroxide ; after mixing, 150 ml. of water is added, followed by 50 ml. of water in which 2·5 gm. of magnesium sulphate has been dissolved and the mixture is heated on a water-bath for 5 minutes and then filtered. The filtrate, which contains the magnesium salts of the free balsamic acids, is then treated in the same manner as the filtrate containing the magnesium salts in the determination of the total balsamic acids.

Pharmacy of Benzoin

The most important galenical containing this drug is compound tincture of benzoin, or Friars' Balsam, which is made by macerating a mixture of crushed benzoin, balsam of tolu, storax and aloes with 90 per cent. alcohol for at least 2 days, filtering and diluting to the required volume with more alcohol. It is a 1 in 10 preparation with respect to benzoin, while one-quarter of this amount of balsam of tolu and three-quarters of the same quantity of storax are employed in its manufacture. The compound tincture is used with hot water for inhalation in bronchitis and inflammatory condi-

Fig. 5.—Determination of total balsamic acids in benzoin

With the evaporation of the last traces of the solvent, the syrupy liquid becomes crystalline.

tions of the pharynx and larynx and is given internally in chronic bronchitis as an expectorant. It is also employed externally as an antiseptic and styptic dressing for small cuts by applying undiluted upon lint. When mixed with water the resinous constituents of compound tincture of benzoin are precipitated, and if the preparation is used as an ingredient of a dispensed medicine it is necessary to add a suspending agent, preferably in the form of a mixture of equal parts of mucilage of acacia and mucilage of tragacanth, such that, together, they form about one-eighth of the total bulk.

BALSAM OF TOLU

This product is obtained from an elegant, lofty, evergreen tree, *Myroxylon Toluifera*, a native of Venezuela and New Granada. The balsam is collected by cutting in the bark two deep sloping notches, meeting at their lower ends in an acute angle. Below the cut, the bark and wood is slightly hollowed out and a calabash of the size and shape of a deep tea-cup is fixed. This arrangement is repeated until many calabashes are applied to the same trunk. The balsam, which is said to take its name from a place called Tolu in a district near Cartagena, is imported as a soft, brown, tenacious, resinous substance, which becomes harder on keeping and is quite brittle in cold weather. The genuine material should contain 19 to 25 per cent. of free balsamic acids and 35 to 50 per cent. of total balsamic acids, both being calculated with reference to the dry alcohol-soluble matter.

The analytical examination of balsam of tolu is conducted by application of the methods already given for benzoin excepting that, as the proportion of alcohol-insoluble matter is small, it is sufficient to dissolve a weighed quantity of the sample in alcohol and filter the solution and, after washing the filter with more alcohol, to dry and weigh the insoluble residue. The free and combined balsamic acids are then determined by applying to the filtrate the method already given for benzoin.

As already mentioned, this balsam is an ingredient of compound tincture of benzoin and this constitutes its most important pharmaceutical application. A syrup, made by adding 40 parts of boiling distilled water to 2·5 parts of the balsam, heating on a water-bath for 30 minutes, allowing to cool, filtering, adding 66 parts of sugar, dissolving by the aid of heat and diluting with more water to make 100 parts by weight, is employed in cough mixtures as a flavouring agent and mild expectorant.

PREPARED STORAX

Storax is obtained from a tree indigenous to Asiatic Turkey, the

secretion of the balsam being induced by beating the bark. The latter becomes saturated with the exudation and is then stripped off, the balsam isolated by pressing, boiling with water, again pressing, and finally separating from the aqueous layer. The product thus obtained forms an opaque, greyish, viscid liquid, which, on standing, separates into a supernatant, aqueous liquid and a dark brown, oleo-resinous layer. This product, which contains 20 to 30 per cent. of water together with fragments of bark, constitutes the storax of commerce and it is converted into prepared storax by dissolving in alcohol, filtering and evaporating the filtrate. Thus purified, it occurs as a translucent, brownish-yellow semi-liquid balsam with a strong aromatic odour and taste.

Prepared storax is composed of a resin mixed with an oily liquid. The resin consists of storesinol, part of which is combined with cinnamic acid, while the oily liquid contains styrol, and various esters of cinnamic acid, in addition to a certain amount of free acid. The total balsamic acids, determined by the method already described under benzoin, should not amount to less than 30 per cent. when calculated with reference to the substance dried on a water-bath for 1 hour. In pharmaceutical practice prepared storax is mainly used as an ingredient of compound tincture of benzoin.

MYRRH, GALBANUM, AMMONIACUM AND ASAFETIDA

At this stage it will be convenient to discuss briefly these four drugs under one heading, since they are all mildly expectorant in physiological action, although they are not all solely employed for this purpose. They belong to a class of substances termed oleo-gum-resins, which are characterised by consisting of a mixture of volatile oil, water-soluble gum and resinous material insoluble in water but dissolved by organic solvents.

Fig. 6.—MYRRH IN TEARS

The two pieces on the left are the two halves of one tear and show the freshly fractured surface.

MYRRH, which is official in the British Pharmacopœia 1932, is obtained by incising the stem of a shrub, *Commiphora molmol*, and is

Fig. 7.—BDELLIUM, SHOWING THE FRESHLY FRACTURED SURFACE

collected in Somaliland. It occurs in irregular, or rounded, or agglutinated tears, externally reddish-brown in colour, rough and often covered with a fine dust. It possesses a pleasant, characteristic, aromatic odour and a bitter taste. The freshly fractured surface is granular, oily and rich brown in colour, and this feature serves towards distinguishing genuine myrrh from other gums and gum-resins with which the imported product is usually mixed. Notable among these other resinous products is bdellium, which has a dull slaty fracture and is devoid of the agreeable odour of genuine myrrh, which is customarily separated from all spurious material by hand-picking. Myrrh contains from 25 to 40 per cent. of resins, 57 to 61 per cent. of a water-soluble gum allied to acacia and from 2·5 to 8 per cent. of volatile oil. When the last-named is isolated and exposed to the air it readily resinifies, producing resin of similar character to that contained in the original myrrh. The drug is officially required to contain not more than 70 per cent. of matter insoluble in 90 per cent. alcohol. The British Pharmacopœia specification includes an identity test, which consists essentially in exposing the residue from an evaporated ethereal extract to the vapours of bromine, when a violet coloration should be produced. Myrrh is mildly expectorant, but in medical practice a 1 in 5 tincture made with 90 per cent. alcohol is mainly employed as an ingredient of mouth-washes for the treatment of spongy gums and aphthous ulcerations. When the tincture is added to lotions or mixtures, mucilage of tragacanth must also be used in order to suspend the precipitated resin.

GALBANUM, like myrrh and many other oleo-gum-resins, was known to the ancients and it is recorded in Exodus that Moses was exhorted to make incense and to take "stacte, and onycha and galbanum: these sweet spices, with pure frankincense: of each shall there be a like weight: And thou shalt make it a perfume, a confection after the art of the apothecary, tempered together, pure and holy." According to Pliny, stacte is a spontaneous liquid exudation of the myrrh tree which was regarded as being even more valuable than myrrh itself, but no substance of modern times has been identified with it. Onycha is the

shell of a species of Oriental mussel used in the composition of perfume. Galbanum is obtained in Persia by cutting the stem or root of *Ferula galbaniflua* and contains about 60 per cent. of resin, 25 per cent. of water-soluble gum and 10 per cent. of volatile oil. It occurs in tears about 10 mm. in diameter, sometimes agglutinated in masses, and of a yellowish or orange-brown colour; the surface is often rough and dirty, and, although hard in cold weather, the tears soften between the fingers. It has a characteristic, aromatic and not unpleasant odour. The drug is employed as a stimulant expectorant in chronic bronchitis and is administered internally in the form of a compound pill which also contains myrrh and asafetida. It is sometimes applied externally compounded with lead plaster in the treatment of inflammatory swellings.

AMMONIACUM originates from the stems of *Dorema ammoniacum*, a plant growing in Persia. The exudation is induced by beetles which puncture the bark, whence some of the gum-resin solidifies in tears on the stems while part of the secretion falls to the ground and forms lumps mixed with earthy matter. Both forms are found in commerce, but for pharmaceutical purposes the tears should be used; they vary in size from about 0·5 to 3 cm. in diameter and are dull pale brown in colour, the freshly fractured surface having a slightly paler milky appearance. Ammoniacum is harder than galbanum and its odour, although characteristic, is not so evident; it contains about 65 per cent. of resinous material and 1 to 2 per cent. of volatile oil, the remainder being water-soluble gum and mineral matter. Taken internally, it facilitates expectoration in chronic bronchitis. It is a constituent of compound squill pill and is also employed as ammoniacum mixture, which contains 3 per cent. of the oleo-gum-resin and 6 per cent. of syrup of tolu triturated together with water; both these preparations were included in the British Pharmacopœia 1914.

Fig. 8.—ASAFETIDA IN TEARS

ASAFETIDA is the dried latex which exudes when the living root of *Ferula fœtida* is cut and is obtained from Eastern Persia and Western Afghanistan. The drug is collected by cutting off the stem close to the crown of the root and it occurs in commerce both in tears and lumps. The tears, which are often aggregated together, are dull yellow in colour

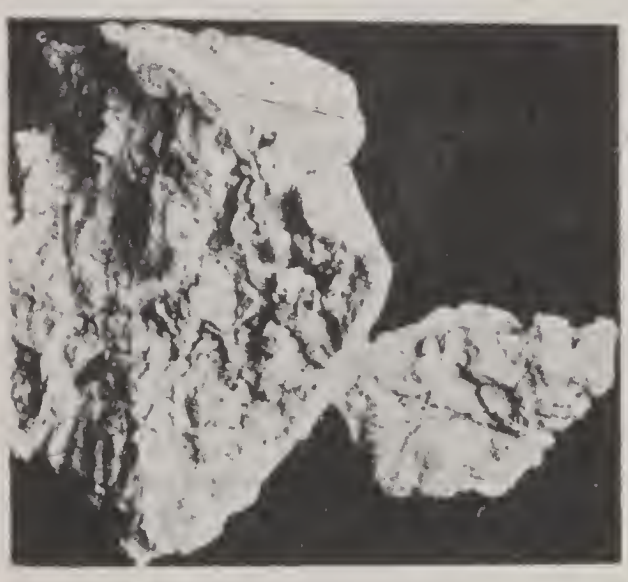


Fig. 9.—Lump asafetida

but become brown on storage, while the freshly broken surface is milky white but soon changes in hue, first to pink and finally to brown. Lump asafetida consists of numerous tears embedded in a brownish matrix and usually contains woody debris and earthy material. Both varieties possess a penetrating, highly objectionable garlic-like odour. Good quality asafetida contains about 60 per cent. of resin, 25 per cent. of gum and 8 per cent. of volatile oil, to which the odour of the drug is due. It is too soft to be powdered until most of the oil has been driven off by drying, but if this is done the drug loses much of its value as a medicine and should not be employed for pharmaceutical purposes. The tincture is used in hysterical disorders on account of its unpleasant smell and taste, but it is also of value as an expectorant and carminative for the treatment of bronchitis. When the tincture is used for dispensing mixtures, mucilage of acacia should be included in order to suspend the precipitated resinous matter.

GRINDELIA

This drug consists of the dried leaves and flowering tops of a perennial herb growing in the plains to the south-west of the Rocky Mountains. It is remarkably resinous in character, containing upwards of 20 per cent. of a mixture of amorphous resins, and has an aromatic bitter taste and slight balsamic odour. Grindelia is used in the treatment of asthma, whooping cough and bronchitis, the most suitable preparation being the liquid extract. This galenical is made by percolating 100 parts of the powdered drug with 90 per cent. alcohol until it is exhausted, recovering the alcohol by distillation, dissolving the residue in 50 parts of distilled water containing 10 parts of sodium bicarbonate to neutralise the acid resin, adding sufficient water to the mixture to make 75 parts and finally diluting with 90 per cent. alcohol to make 100 parts by volume. If this preparation is intended to be used in warm climates the proportion of alcohol should be increased to one-fourth by weight of the finished product in order to inhibit fermentation. The liquid extract is prescribed in mixtures containing one-sixteenth their volume of mucilage of acacia to prevent separation of resinous substances. The nauseous taste may be disguised with spirit of chloroform or liquid extract of liquorice.

COCILLANA

This is the bark of a large Bolivian tree, *Guarea Rusbyi*, and is sometimes referred to as Guapi bark. Although its therapeutic value as an expectorant was discovered some 50 years ago it has been little used, although, recently, interest in the drug has revived. It is stated to closely resemble ipecacuanha in its physiological action but to be somewhat more stimulating. A 1 in 1 liquid extract made with 60 per cent. alcohol is used in the formulation of an effective compound syrup which also contains liquid extracts of euphorbia, squill and senega together with potassium antimonyl tartrate, codeine phosphate, menthol, spirit of chloroform and glycerin.

EUPHORBIA

This drug, which consists of the entire aerial portion of *Euphorbia pilulifera*, an annual herb growing in most tropical countries, has already been mentioned as being used in association with cocillana. The principal constituent is thought to be an unstable glucoside which, however, has not been isolated. It is occasionally used in the form of the decoction for the treatment of asthma and bronchitis, while the liquid extract and tincture are sometimes prescribed in mixture form generally with squill and senega.

HOREHOUND (MARRUBIUM)

White horehound (*Marrubium vulgare*), which is indigenous to Britain and is widely distributed over Europe, is characterised by its bushy stems, up to 2 feet high, which are covered with woolly down, its wrinkled leaves and its dense whorls of small white flowers of which the calyx teeth are sharp and hooked. The drug, which consists of the dried leaves and flowering tops, has an agreeable odour and somewhat aromatic and bitter taste. It contains a crystalline bitter principle, marrubiin, together with a little volatile oil and tannin. It is a useful expectorant and a popular remedy for coughs, colds and pulmonary affections.

Syrup of horehound is made by digesting on a water-bath 42·5 parts of the drug with boiling water for an hour, straining, pressing and evaporating the expressed liquor until it measures about 47 parts, when it is allowed to cool. It is then filtered, 85 parts of sugar are added, the mixture gently warmed until complete solution is effected and, finally, the specific gravity of the cooled syrup is adjusted to 1·330. Oxymel of horehound is another useful preparation. It is made by digesting on a water-bath 42·5 parts of the drug with sufficient boiling water to cover it, pressing out the aqueous extract, evaporating until it measures about 50 parts, allowing to cool, adding 6·75 parts of acetic acid (33 per cent.), filtering and making up to 100 parts with clarified honey. Various

preparations and extracts of horehound find their way into proprietary cough mixtures and lozenges, often in association with demulcent drugs such as coltsfoot (see Table XV, page 229) and extract of liquorice.

OTHER EXPECTORANT VEGETABLE DRUGS

A further selection of drugs of very minor importance, preparations of which, nevertheless, may occasionally be met with in connection with the compounding of cough mixtures or medicines for the treatment of respiratory disorders, are listed in Table XI.

TABLE XI—VEGETABLE DRUGS OF MINOR IMPORTANCE OCCASIONALLY USED FOR RESPIRATORY COMPLAINTS

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Remarks*
Bryony (Bryoniæ Radix)	Root ..	Tincture	Given in small doses to relieve the pain and cough of pleurisy; in large doses it is a cathartic and diuretic.
Elecampane (Inula)	Root and Rhizome	Decoction ..	Rarely used; contains a bitter principle, iso-alantolactone or helenin, which is said to act as an antiseptic in bronchitis, etc.
Eriodictyon (Eriodictyon)	Leaf ..	Liquid Extract ..	Main active constituents are phenolic compounds; the drug is used for asthma.
Poppy Capsules (Papaveris Capsulæ)	Fruit ..	Liquid Extract and Syrup	This drug comes from *Papaver somniferum* and contains about 0·2 per cent. of morphine.
Sanguinaria (Sanguinaria)	Rhizome ..	Tincture	This drug contains an alkaloid sanguinarine, which belongs to the opium group having a physiological action midway between that of codeine and thebaine.
Tylophora (Tylophoræ Folia)	Leaf ..	Tincture	Used in India and the East as an expectorant in place of ipecacuanha.

QUEBRACHO OR ASPIDOSPERMA

Although not an expectorant quebracho has a remarkable stimulating action on the respiratory centre and a brief notice of the drug may make

a fitting close to this chapter. It consists of the dried bark of a large evergreen tree growing in the dry central and western districts of the Argentine and contains a number of alkaloids, one of which, quebrachine, is stated to be identical with yohimbine (see page 150). However, galenical preparations of the drug are not employed as aphrodisiacs but as ingredients of tonics and antipyretics. The marked influence on the respiration has suggested the use of quebracho in the treatment of dyspnœa (difficulty in breathing), particularly where this arises from pulmonary disease ; but it would appear that the administration of the drug does not lead to a reliable response, possibly because certain of the alkaloids possess antagonistic physiological action. Thus it has been reported that, whereas quebrachine has an action antagonistic to that of adrenaline, quebrachamine does not act similarly to quebrachine but, on the contrary, reinforces and prolongs the action of adrenaline. It may be that future pharmacological investigations will result in some useful application of one or more of the many alkaloids contained in this interesting drug.

Chapter XVIII

DRUGS CONTAINING TANNINS

THE drugs in this group are mainly used for their astringent property, which is due to the tannins which they contain. The tannins constitute a large class of substances occurring in many plants which are distinguished by having an astringent taste, giving a blue-black or green coloration when mixed with ferric salts and the formation of a precipitate when added to proteins such as gelatin or albumin. The tanning of hides to form leather depends upon the last-mentioned characteristic.

OAK GALLS

Commercial tannic acid, or gallotannic acid, which will be described later, is obtained from galls which occur as excrescences on the twigs of various species of oak, but particularly on *Quercus infectoria*, a small tree native to Asia Minor and Persia. Galls are produced as a result of irritation to the growing shoots caused by the gall-wasp. The female insect introduces its eggs between the rudimentary leaves near the growing point of a shoot. The young larvæ feed upon the tissues of the plant and at the same time secrete a fluid which stimulates the cells of the plant tissues to rapid division, resulting in the formation of galls. Within these galls the larvæ pass through the pupa stage, and the wasps, as soon as they emerge, escape by piercing holes with their mandibles. The galls most esteemed in commerce are collected before they have been perforated and are known as Aleppo blue galls, although their actual colour is dark olive-green. They are almost spherical and about 1·5 cm. in diameter. The perforated variety are yellow or brown and have a central cavity, which, in unperforated galls is occupied by the remains of the insect. Aleppo galls contain from 50 to 70 per cent. of tannic acid, while galls obtained from English oak trees, which are brown and smoother, contain only 15 to 20 per cent.

Aleppo galls are employed in medicine for their astringent properties, mainly in the form of an ointment for the treatment of hæmorrhoids. For this purpose they are finely powdered and mixed with benzoinated lard, while it is sometimes advantageous to incorporate powdered opium with the gall ointment to mitigate pain.

OAK BARK

Another important source of tanning material is the bark of the English oak. Good qualities contain 15 to 20 per cent. of quercitannic

acid, which, like gallotannic acid, is capable of precipitating proteins and is, therefore, effective for making leather. The oak is cultivated in this country for its bark, which, while still smooth, is stripped in May and dried. It occurs in thin strips of varying length and about 2·5 cm. wide. The outer surface is glossy and silvery-grey and generally marked with darker coloured transverse lenticels, while the inner surface is brown.

CHEMICAL CLASSIFICATION OF TANNINS

The tannins have been divided into the following three groups, according to their behaviour when treated with boiling dilute sulphuric acid :—

(*a*) The Depside-tannins, which hydrolyse with the formation of gallic acid (trihydroxy-benzoic acid).

(*b*) The Ellagi-tannins, which form a precipitate of ellagic acid.

(*c*) The Phlobo-tannins, which produce an amorphous red precipitate of phlobophane.

The depside-tannins yield a blue-black colour or precipitate with ferric salts and chemically are derivatives of pyrogallol (pyro). Ordinary tannic acid obtained from galls or sumach and used for tanning hides belongs to this group. The ellagi-tannins are relatively rare and unimportant. The active principles of the drugs about to be considered belong to the phlobo-tannins, which are derivatives of catechol (one of the dihydroxy-benzenes) and generally give a green colour when treated with ferric salts. The tannin of tea belongs to this group.

CATECHU

This drug is also known under the names Pale Catechu, Gambir and Gambier. It must be carefully distinguished from Cutch or Black Catechu, which will be described separately. Catechu is an extract prepared by evaporating an aqueous decoction of the leaves and young shoots of *Uncaria Gambier*, a climbing shrub indigenous to the Malay Archipelago. While the decoction is being evaporated to a syrupy

Fig. 1.—Pale catechu or gambier

The circles impressed on the cubes are a brand mark and are not characteristic of the drug. Catechu is imported in cases containing 100 packets each consisting of 100 cubes.

consistency in copper pans, it is agitated by means of a stick which is moved up and down in an oblique direction in order to induce crystallisation. When the consistency of the residue approximates to that of soft clay it is transferred to trays, cut into cubes from 2 to 3 cm. square and dried ; more rarely it is cut into strips or discs. Externally, cubes of catechu are dark reddish-brown in colour, while the interior is pale cinnamon-brown. The drug is friable and without odour, while the taste is at first bitter and astringent, but afterwards sweetish.

Chemistry of Catechu

Catechu consists largely of catechin and catechutannic acid. There is usually about 10 per cent. of moisture, together with smaller quantities of catechu-red, quercetin, wax, oil, mineral matter and a characteristic fluorescent body known as gambier-fluorescein. Catechin occurs as white acicular crystals, which are sparingly soluble in cold water, but freely dissolve in boiling water. It has the formula $C_{15}H_{14}O_6.4H_2O$ and melts at 96° C. A solution of catechin gives an intense green colour on the addition of a few drops of ferric chloride solution. In the presence of caustic alkalis and water, catechin is readily oxidised with the formation of a black dye, while under similar conditions the alkali carbonates induce the formation of a red dye. This property is important industrially and has led to the extensive use of catechu for dyeing.

Catechutannic acid occurs as a reddish amorphous substance, soluble in cold water. It is considered to be chemically related to catechin and to differ only by the loss of the elements of one molecule of water of constitution. It precipitates gelatin, and its solutions are coloured dirty green by ferric chloride. When its aqueous solutions are boiled, insoluble catechu-red is precipitated. The proportions of catechin and catechutannic acid present in catechu differ considerably, and may vary from 7 to 33 per cent. of the former and 22 to 50 per cent. of the latter, but much depends upon the way in which the original decoction is evaporated.

Tests Applied to Catechu

The proportion of the drug soluble in 90 per cent. alcohol should not be less than 70 per cent. At least 75 per cent. should be soluble in water and it should not leave on incineration more than 8 per cent. of ash. When an alcoholic extract is made strongly alkaline by the addition of sodium hydroxide, the mixture shaken with petroleum ether and the immiscible liquids allowed to separate, the upper petroleum layer shows a brilliant green fluorescence. This is due to the presence of gambier-fluorescein, and since this compound is absent from cutch, or black catechu, the test is sometimes important for identification purposes.

Methods for the evaluation of this drug are directed to the deter-

mination of catechutannic acid and a process for effecting this will be given in the description of cutch, since the same procedure is applicable to both products.

Pharmacy of Catechu

Catechu is frequently administered in association with other astringent drugs in the form of compound powder of catechu which contains 40 per cent. of catechu, together with 20 per cent. each of kino and krameria and 10 per cent. each of cinnamon bark and nutmeg. Cachets, each containing 10 grains of this powder, are used in the treatment of diarrhœa.

The tincture of catechu is made by treating a mixture of crushed catechu and bruised cinnamon with 45 per cent. alcohol by the maceration process. Five parts of the tincture should contain the active principles of one part of catechu. The tincture is frequently prescribed in conjunction with tincture of opium, tincture of ginger and compound aromatic powder ; this latter is a mixture of powdered sugar with cinnamon bark, nutmeg, saffron, cloves and cardamom seeds.

Catechu lozenge, containing one grain of the drug in a basis of black currant paste, sugar and a little gum tragacanth, is a useful medicament for the throat.

CUTCH OR BLACK CATECHU

This substance, which is regarded by some authorities as the true catechu, is the extract obtained by evaporating an aqueous decoction of the heartwood of *Acacia Catechu*, a tree common in India and Burma. After the tree has been felled and the bark and sapwood removed from the trunk, the heartwood is cut into chips and boiled with water. The decoction is then strained, evaporated to a syrupy consistency and spread upon leaves arranged within wooden moulds, where it is allowed to set. It occurs in commerce as odourless, brittle, dark brown or nearly black, irregular masses, to which pieces of leaves or paper are often found adhering.

Fig. 2.—Cutch or black catechu

The illustration shows the remains of leaves which have been used for wrapping purposes.

Chemistry of Cutch

The principal constituents are

catechutannic acid and acacatechin, the empirical chemical formula of which is $C_{15}H_{14}O_6.3H_2O$, and it is regarded as being a different substance from catechin, which, however, it closely resembles. Quercetin, catechu-red and mineral matter are also present, but gambier-fluorescein is absent. Good quality cutch should be almost entirely soluble in boiling water and about 60 per cent. should dissolve in 90 per cent. alcohol.

Identification Test for Acacia Cutch

The following simple test distinguishes the cutch of *Acacia Catechu* from that derived from mangrove bark :—

A few drops of a fresh aqueous extract of the sample is added to about 10 ml. of lime water. Under these conditions, acacia cutch gives a brown coloration, changing to a red precipitate in the course of 3 minutes, while mangrove cutch yields a red precipitate at once. Catechu from *Uncaria Gambier* may give a turbidity, but no precipitate, within 3 minutes.

Determination of Tannin in Catechu and Cutch

It has been shown by David Hooper that the determination of catechu-tannic acid is best conducted by an appropriate modification of A. Chaston Chapman's cinchonine method. The process is carried out in the follow-ing manner :—

About 0·4 gm. of the powdered sample is accurately weighed and treated with warm water, the volume being made up to 100 ml. Exactly 50 ml. of this extract is filtered off, the filtrate is transferred to a beaker and 50 ml. of a saturated aqueous solution of cinchonine sulphate added. The catechutannic acid is precipitated as the insoluble cinchonine salt. After standing for about an hour the precipitate is collected in a tared Gooch crucible. In this filtration it is best to commence without connecting the suction pump, the latter only being applied when most of the liquid has passed through.

The precipitate is washed with a half-saturated aqueous solution of cinchonine sulphate and when all superficial liquid has been removed from the precipitate in the crucible, the latter is placed on a porous plate until the next day and then finally dried at 100° C. The weight of the precipitate multiplied by 0·6 gives the weight of catechutannic acid in half the amount of sample taken at the commencement of the assay.

Determination of Catechin

The content of either catechin or acacatechin may be determined with fair accuracy by taking advantage of the fact that both compounds are soluble in hot, but nearly insoluble in cold, water. An alcoholic extract of a weighed portion of the sample is evaporated to dryness and the residue

dissolved in a little hot water. When the solution is quite cold the crystals of catechin or acacatechin are collected by filtration through a tared Gooch crucible, washed with ice-cold water, dried at about 90° C. and weighed.

Results of the Analysis of Cutch

A selection of analytical results obtained by David Hooper is given in Table XII.

TABLE XII.—RESULTS OF THE ANALYSIS OF CUTCH

Variety of Sample	*Acacatechin per cent.*	*Catechutannic Acid, per cent.*	*Ash per cent.*
From Cawnpore	43·4	16·6	0·6
From Surat	10·6	4·5	47·0
From Shirval (powder)	13·8	44·0	2·0
From Burma (for dyeing) ..	12·4	17·1	33·2
From Burma (for dyeing) ..	15·0	44·5	2·3
Unknown origin	1·0	0·3	78·0

It is seen that the composition of commercial cutch varies very considerably. This variety of catechu is used more in the dyeing and tanning industries than in pharmacy, but when employed for medicinal purposes it is compounded similarly to gambier-catechu.

KINO

There are several varieties of kino, but when the word is used without any qualifications it is assumed to refer to Malabar, or Cochin, kino, which is the juice obtained by incision from the trunk of *Pterocarpus Marsupium*. This tree grows in southern India and Ceylon, and when the bark is cut a treacly liquid exudes which is collected, boiled, dried and crushed. It readily breaks up into small brittle angular grains of a dark ruby-red colour.

Chemistry of Kino

Kino contains about 75 per cent. of a phlobo-tannin called kinotannic acid ; this is soluble in water, but an oxidation product of kinotannic acid, called kino-red, which is also present in varying proportions, is insoluble. Good quality kino should contain at least 75 per cent. of water-soluble matter. Kino also contains small quantities of catechol, gallic acid, and about 13 per cent. of moisture.

Freshly filtered aqueous solutions of kino often gelatinise, owing to the precipitation of insoluble kino-red formed by oxidation. This change is induced by the presence of an oxydase enzyme and may be arrested by boiling the fresh solutions. The boiling of the juice when freshly collected is intended to mitigate the formation of kino-red.

Pharmacy of Kino

The tincture is made by triturating the drug with three and a half times its weight of a mixture of 3 parts of glycerin and 5 parts of water, then adding alcohol and allowing to macerate for 12 hours. The mixture is filtered through cotton-wool and diluted with more alcohol to form a 1 in 10 tincture. This galenical is liable to gelatinise during storage, and it is stated that a better preparation may be made by adding kino to five times its weight of boiling water, maintaining the mixture at the boiling point for half an hour, replacing the water lost by evaporation, diluting with alcohol to produce a 1 in 10 tincture, and straining after 12 hours.

Tincture of kino is frequently used in association with chalk mixture as a remedy for diarrhœa.

Compound powder of kino, containing 75 per cent. of kino together with powdered cinnamon bark and opium, is employed as an intestinal astringent.

OTHER VARIETIES OF KINO

There are several other red astringent juices resembling Malabar kino which are obtained from plants belonging to various natural orders. They are used in the same manner as the kino already described and all contain phlobo-tannins. Mention may be made of the two more important members of the series.

EUCALYPTUS KINO is obtained from various species of Australian eucalyptus trees. It is often termed red gum and occurs in commerce as dark red irregular pieces about 1 cm., or less, in diameter. Besides about 40 per cent. of tannin bodies, it contains variable proportions of kino-red, catechin, catechol and moisture. If an aqueous extract is boiled for a minute with a slight excess of tincture of iodine, and the mixture then cooled, the precipitate which forms is soluble in dilute ammonia solution, while that produced by Malabar kino under the same conditions is insoluble.

BUTEA GUM is a juice which originates from the stem of the Indian tree, *Butea frondosa*. The small irregular grains often have fragments of the

original cork and cortex of the stem attached to them. It contains kinotannic acid and is used in India and the Eastern Colonies in place of Malabar kino. It is frequently referred to as Bengal kino.

KRAMERIA OR RHATANY

This drug consists of the dried root of *Krameria triandra*, a plant native to Peru and Bolivia. It is generally known in commerce as Peruvian Rhatany. The root occurs in odourless, dark reddish-brown pieces of varying size, covered with a scaly fibrous bark. Another variety of Krameria, known as Para Rhatany, is obtained from *Krameria argentea*, a plant growing in Brazil. The root is much thinner than that of the Peruvian species and is characterised by numerous transverse cracks and the dark purplish-brown colour of its bark. Para Rhatany is not included in the present British Pharmacopœia.

Fig. 3.—KRAMERIA OR RHATANY ROOT
This shows the Peruvian variety. The pieces vary considerably in size. It is imported in bales each weighing 200 lb.

Chemistry of Krameria

The active principle is krameriatannic acid; it is stated that the whole drug contains from 7 to 9 per cent., most of which is in the bark. There is also present a dark red phlobophene termed krameria-red, produced by the oxidation of krameriatannic acid. This probably corresponds to the kino-red derived from kinotannic acid. Other constituents include starch and mineral matter.

Pharmacy of Krameria

Tincture of krameria is made by the standard percolation process, using 60 per cent. alcohol. It is used internally as an astringent and, when diluted with water, makes a useful mouth-wash for inflamed gums.

Dry extract of krameria, which is employed in the preparation of lozenges, consists of the dry residue resulting from the evaporation, under reduced pressure, of an aqueous percolate of the powdered drug.

Lozenge of krameria is made by adding the dry extract to sucrose and gum acacia, both in fine powder, adding a little tincture of tolu and making into a paste with water. After cutting, the lozenges are dried in a hot-air chamber. Each lozenge should contain 1 grain of dry extract of krameria. Lozenge of krameria and cocaine is similar, but contains, in addition, one-twentieth of a grain of cocaine hydrochloride, and is used for the relief of coughs arising from relaxed sore throat.

HAMAMELIS OR WITCH HAZEL

Both the bark and the leaves of witch hazel are used in pharmacy. *Hamamelis virginiana* is a shrub native to the United States and Canada. The bark occurs in thin pinkish pieces, usually 8 or 10 cm. long, often exhibiting grey areas where the cork remains adherent. The pinkish inner surface of the bark is variegated with portions of white woody material. The leaves are about 15 cm. long by 10 cm. broad, and have a sinuate margin. They are usually dark green or brown in colour and the lateral veins run straight from the midribs to the edge of the leaves.

Fig. 4.—HAMAMELIS OR WITCH HAZEL BARK

The greyish areas of cork tissue on the exterior and the light coloured woody material of the inner surface are characteristic features of this drug.

Chemistry of Hamamelis

The bark contains about 6 per cent. of tannin, part of which has been isolated into a crystalline body termed hamameli-tannin. Small quantities of gallic acid, resin, and fat are also present. The leaves contain, in addition, traces of volatile oil.

Pharmacy of Hamamelis

Liquid extract of hamamelis is made from the powdered leaves by the standard percolation method, using 45 per cent. alcohol. When the extract is mixed with nine times its weight of hydrous wool fat it forms an ointment valuable for its local astringent and hæmostatic properties in the treatment of piles. Solution of hamamelis, or distilled witch hazel, is prepared by mixing the fresh leaves with twice their

weight of water, adding a little alcohol and, after allowing to macerate for 24 hours, distilling half the liquor. It is imported from the United States as a clear, colourless liquid. It forms a useful astringent and mild antiseptic for abrasions, and when diluted with water it is employed as a spray in acute coryza and also constitutes a favourite ingredient of astringent eye lotions.

Hamamelin is the name given to a dry alcoholic extract of the bark or leaves. It occurs as a hygroscopic brown powder. The yield from the leaves is about 7 per cent., while that from the bark is approximately 16 per cent., but the former is said to be a more effective astringent. Hamamelin is chiefly used for making suppositories for the treatment of piles. For this purpose it is incorporated into oil of theobroma and often combined with other medicaments such as cocaine, extract of belladonna or bismuth subgallate.

Fig. 5.—Witch hazel leaves

The sinuate margins and disposition of the lateral veins should be noted.

THE MECHANISM OF ASTRINGENT ACTION

Before closing our account of this group of vegetable drugs, a few words may be added upon the subject of their pharmacological action. If an aqueous solution of a tannin is added to a neutral or slightly acid solution of a protein, such as albumin or gelatin, an insoluble precipitate is produced. Similarly, if a tannin solution is applied to a living mucous membrane a fine pellicle of precipitated protein is produced, which accounts for the feeling of constriction and roughness in the mouth following the drinking of preparations containing tannins. In the stomach tannins combine with any protein substance with which they come in contact and form precipitates but, as digestion proceeds, these insoluble compounds are broken down again and the tannins pass into the intestines, where they again precipitate the proteins lining the walls of the gut. This results in a partial arrest of the peristaltic movements and accounts for the value of the tannin group of drugs in the treatment of diarrhœa.

OTHER ASTRINGENTS

A few additional members of the tannin series are summarised in Table XIII.

TABLE XIII.—A SELECTION OF ASTRINGENT VEGETABLE DRUGS OF SECONDARY IMPORTANCE

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Remarks*
Bael Fruit or Indian Bael (Belæ Fructus)	Fruit ..	Liquid Extract	The half-ripe fruit is employed. The drug is mildly astringent and is used in India for the treatment of diarrhœa and dysentery.
Coto or Paracoto (Coto)	Bark ..	Tincture ..	Used in the treatment of diarrhœa and for the prevention of cholera when the tincture is sometimes prescribed with aromatic sulphuric acid, the compound tinctures of camphor and chloroform and flavouring.
Elm Bark (Ulmi Cortex)	Bark ..	Decoction ..	This is derived from the common elm tree, *Ulmus campestris*, and should not be confused with slippery elm, the bark of *Ulmus fulva*.
Hemlock Spruce Bark (Pini Canadensis Cortex)	Bark ..	Liquid Extract	Used as an astringent douche for the treatment of leucorrhœa.
Logwood (Hæmatoxyli Lignum)	Wood ..	Decoction and Liquid Extract	Logwood is a useful drug for the treatment of diarrhœa. It is sometimes administered in association with catechu.
Myrobalans (Myrobalanum)	Fruit ..	Ointment ..	Used as the equivalent of galls in India and the Eastern Colonies.
Pomegranate Rind (Granati Fructus Cortex)	Pericarp of Fruit	Decoction ..	This is derived from the same tree as the anthelmintic drug, pomegranate bark. The rind of the fruit is a powerful astringent and may contain about 30 per cent. of tannin.
Sappan (Sappan)	Wood ..	Decoction ..	Used in India and the Eastern Colonies as a substitute for logwood.
Willow Bark (Salicis Cortex)	Bark ..	—	This drug is obtained from *Salix alba* and other species of *Salix*. Salicin is generally extracted from *S. fragilis* which is largely grown in Belgium. It is the source of Salicin.

TANNIC ACID

As already mentioned, gallotannic acid, or ordinary tannic acid, is obtained from galls. It occurs as a yellowish or light brown powder, or in small glistening scales. It has a faint odour and strongly astringent taste, and is easily soluble in water, forming an acid solution which gives a deep bluish-black colour on the addition of ferric chloride.

The Tannic Acid Treatment of Burns

Tannic acid now finds a most important application in medicine for the treatment of severe burns and scalds. The treatment, which was first introduced in 1925 by E. C. Davidson, of the Henry Ford Hospital at Detroit, consists in repeatedly spraying the burned area with a freshly prepared 2·5 per cent. aqueous solution of tannic acid. The first effect of a severe burn is to produce the symptoms of shock due to stagnation of the blood in the capillary system of the body and consequent fall in the blood pressure. After recovery from this condition and with ordinary dressing of the burns, progress would be satisfactory for a while ; in a large percentage of cases, however, this was followed by distressing symptoms of toxæmia with rise of temperature and restlessness, often developing later into unconsciousness and death. This poisoning has been shown to be due to absorption from the burned area of toxic substances produced by the damaged tissues. These toxins are proteins, and by using a tannic acid spray they are immediately coagulated into insoluble and unabsorbable compounds, and the dreaded toxæmia does not supervene. At the same time a hard crust is formed over the damaged area, thus providing an ideal condition for the growth of new tissue underneath. Therefore only the lightest of bandages are employed and in simple cases it is only necessary to wait for the scab of burned and tanned tissue to peel off gradually as healing progresses underneath.

Following upon the announcement by E. C. Davidson of this method for the treatment of burns, a considerable amount of research was conducted in this country.

It was found that it is better to increase the strength of the tannic acid solution to 20 per cent. and also to incorporate 0·1 per cent. of acriflavine. Acriflavine is a powerful and non-irritating germicide. In applying this modification, the blistered and devitalised epidermis is first removed and the raw surface painted with the tannic acid-acriflavine solution and the area then dried with a current of hot air. A second application is usually necessary, particularly when the areas have been cleansed with normal saline solution, while a modification which has found some favour consists in following the initial tannic acid treatment with a spray consisting of a 10 per cent. aqueous solution of silver nitrate.

A jelly containing 5 per cent. of tannic acid in a mucilage of tragacanth is included in the Third Addendum to the British Pharmacopœia under the name Pasta Acidi Tannici. Similar preparations bearing proprietary names have long been on the market, and they are widely used for first-aid purposes.

Chapter XIX

ANTHELMINTIC DRUGS

ANTHELMINTIC drugs are substances used to kill or remove intestinal worms. They are often divided into vermicides and vermifuges, according as they kill or merely cause the expulsion of the worm, but this is determined largely by the quantity which comes in contact with the parasite and the rapidity with which the bowel is evacuated.

MALE FERN (FILIX MAS)

This consists of the dried rhizome of a fern, *Dryopteris filix-mas*, which is indigenous to Great Britain. In commerce the dried rhizome occurs in pieces from 7 to 15 cm. or more in length and about 5 cm. in diameter, covered with the dark brown bases of the fronds which bear numerous brownish membranous hairs. In the parenchymatous tissue of both rhizome and frond bases there are axially elongated intercellular cavities into which glandular hairs project ; covering these hairs is a resinous secretion in which the physiologically active constituents are contained. The latter consist of a group of substances known collectively as filmarone, or filicin, which are all acidic in character and form water-soluble compounds with alkali and alkaline earth hydroxides ; however, the precise chemical constitution of these substances does not appear to be known.

Pharmacy

Male fern is almost invariably administered in the form of the extract which is made by exhausting the coarsely powdered rhizome with ether, recovering the solvent from the percolate by distillation and evaporating the residue on a water-bath until it acquires a thick, oily consistency. The Pharmacopœia specifies that it should be assayed for its content of filicin and, if necessary, adjusted to contain between 24 and 26 per cent. by weight either by further evaporation or dilution with olive oil. The finished product is a thick, dark green liquid, frequently containing a granular sediment, and it is administered in gelatin capsules, the usual dose varying from 45 to 90 minims.

Determination of Filicin

A weighed quantity of the extract is dissolved in ether, the solution transferred to a separator, a measured quantity of a 3 per cent. aqueous

solution of barium hydroxide added and the mixture well agitated. After allowing the two liquids to separate the lower aqueous layer is drawn off through a filter, a measured aliquot part of the filtrate being transferred to another separator, the liquid acidified with hydrochloric acid and the liberated filicin extracted by shaking with successive portions of ether. The ethereal extracts are filtered into a tared flask, the solvent distilled off and the brownish coloured residue of filicin dried at 100° C. and weighed. Barium hydroxide is employed as the alkali rather than soda or potash because it does not form soluble soaps with the fatty acids naturally present in male fern extract : calcium hydroxide, which might otherwise be used, is not sufficiently soluble in water.

Therapeutic Use

Extract of male fern is employed almost exclusively for the expulsion of tape worms, the normal practice being to effect a preliminary purge with magnesium sulphate, then, after a few hours, to administer not less than 40 minims of the extract and 4 hours later a full dose of castor oil. Instead of being administered in capsules, extract of male fern may be dispensed as an emulsion prepared by mixing it with a sixth of its volume of tincture of senega, about an equal weight of powdered gum acacia or half its weight of compound powder of tragacanth and water.

Notes on Tape Worms

Anatomically, a tape worm, or flat worm, consists of a small head and neck, which together form the scolex, and a ribbon-like colony of segments or proglottids. In *Tænia saginata*, the commonest form infesting man, the head, which is about 1/15 inch in diameter, is followed by the thin neck and then by a long succession of segments numbering many hundreds and gradually increasing in size so that the whole colony, or strobila, may be anything up to 30 feet long. The head is provided with four suckers which effect its firm attachment to the intestinal walls of the host. There is no alimentary system, since the tape worms absorb their nourishment directly through any part of their body. Each segment is a sexually complete organism, producing ova and also the sperms to fertilise them. The mature proglottids may either expel their eggs into the fæces of the host or, as is common, break off and pass out, when they, or the expelled eggs, may be eaten by some animal and in this way effect an entrance into an intermediate host where the eggs can develop into the larval stage. Within each egg is a six-hooked embryo which escapes into the alimentary canal and works its way into the muscles or liver, there to become encysted into a bladder-like structure about a quarter of an inch across called a cysticercus. The ox is the intermediate host of *Tænia saginata* and when man ingests a live cysticercus as a result of eating raw or imperfectly cooked meat

the adult stage becomes established in the alimentary canal in about two months, and the life cycle of the parasite is thus completed.

Tænia solium is the name given to the tape worm contracted as a result of eating " measly pork." It is smaller than *T. saginata* and differs

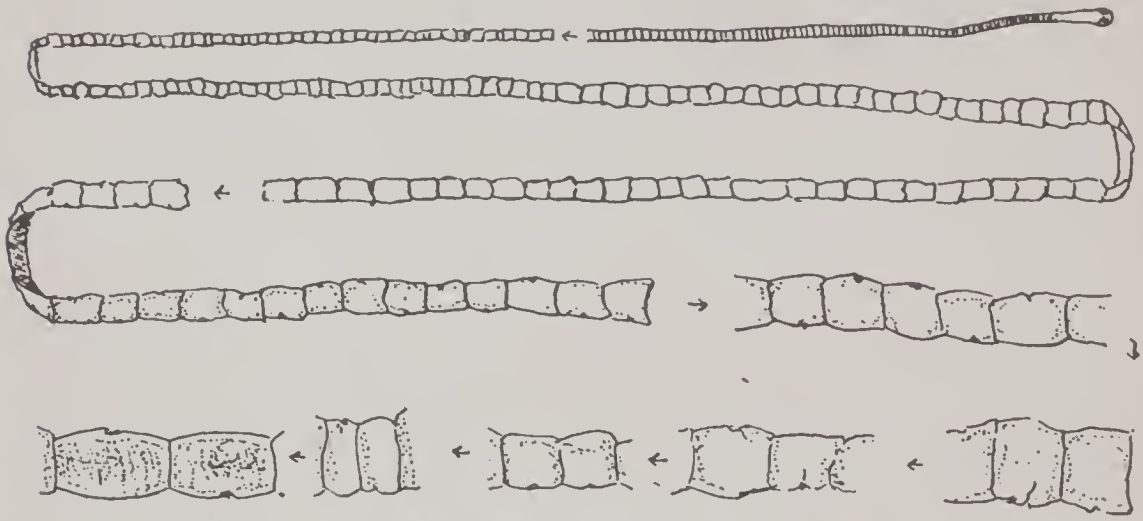


Fig. 1.—THE COMMON BEEF TAPE WORM, TÆNIA SAGINATA

Only portions of the long chain of proglottids are shown, the gaps being indicated by arrows. The genital apertures on the sides of the segments become more evident as they approach maturity in the older and larger members of the series.

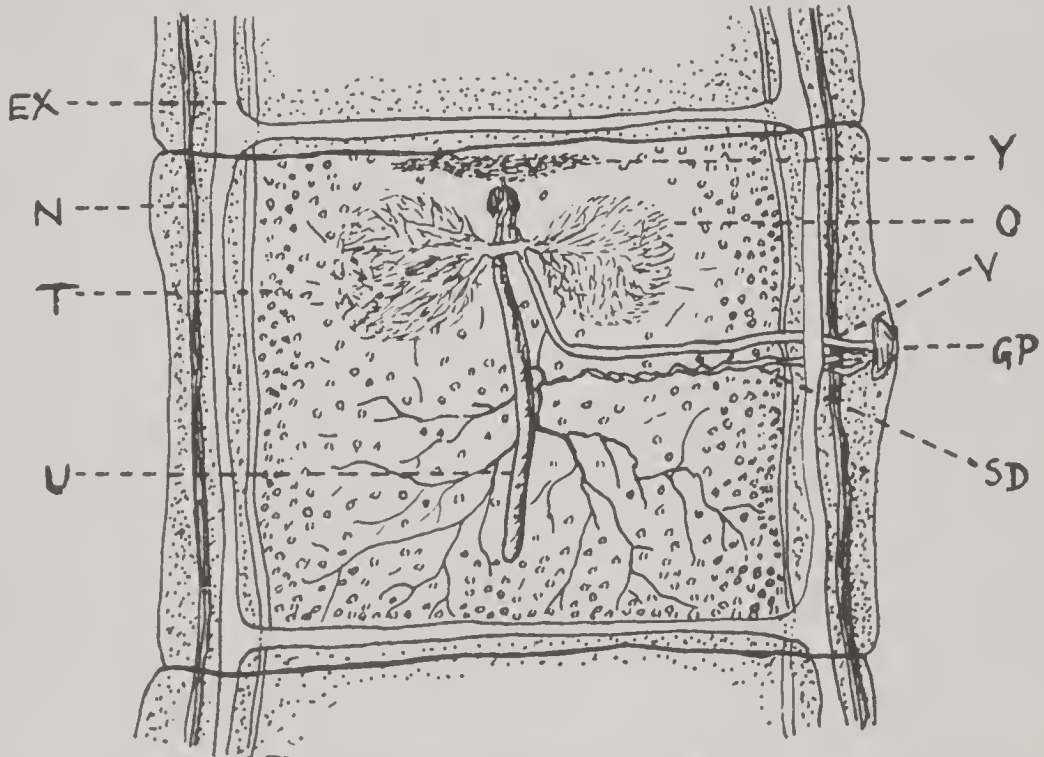


Fig. 2.—MATURE PROGLOTTID OF THE COMMON BEEF TAPE WORM

This diagram shows a segment enlarged about 5 diameters. N, nerve cord; T, testis; Y, yoke gland; O, ovary; G.P, genital pore; S.D, sperm duct; V, vagina; U, uterus; EX, excretory canal.

from it in having a globular head about 1/25 inch in diameter with a rostellum which is crowned by 26 to 28 hooklets (see Fig. 3). The segments of both kinds are superficially similar but the detailed markings, due to the anatomical characteristics of the uterus, differ and constitute the best diagnostic test for establishing the type. The cysticercus finds its ideal habitat in the tongue, neck or shoulder muscles of the hog, but an intermediate host is not essential and, should a human being chance to carry eggs on his fingers to his mouth as a result of examining mature segments the larval stage may become established in the primary host. The cysticercus tends to invade the brain or the eye and so is liable to cause convulsions, death, or blindness, particularly as the cysts, which are normally about the size of a pea, sometimes become as large as walnuts when developing in brain tissue. Thus an infection with *T. solium* is fraught with some danger but fortunately its occurrence is rare. In contrast, whereas *T. saginata* is much more common, yet, owing to the essential need for the larval stage to develop in an intermediate host, an infection does not generally result in anything worse than discomfort and a moderate degree of debility. In some localities in Africa and Syria, and also among Tibetans, one-fourth to one-half of the inhabitants are infected. A full dose of male fern extract may result in yards of strobila being expelled but, should the treatment fail to kill or remove the head, many hundreds of fresh segments will develop in a few weeks and treatment may have to be repeated several times.

Fig. 3—Scoleces of tape worms
Note the small hooks surrounding the head of *T. solium*, A. The head of *T. saginata* is shown at B. Both magnified about 10 diameters.

Altogether, twenty-five different species of tape worms have been recorded as attacking man, but there are perhaps only three others that are of frequent occurrence, namely : *Diphyllobothrium latum*, or "fish tape worm," a large type common to the northern United States, which is transmitted through fish as the intermediate host ; *Hymenolepis nana*, or dwarf tape worm, which is rarely more than about 2 inches in length, though usually many will be present in an infected person ; finally, *Echinococcus granulosus*, a minute species occurring in dogs, and which produces a larval cycle of enormous size which infests ruminant animals and man as intermediate hosts, and are then known as hydatid cysts.

POMEGRANATE BARK (GRANATI CORTEX)

This drug is obtained from the stem and root of a small tree indigenous to North-Western India and cultivated in the countries bordering the Mediterranean. The bark contains several alkaloids, the most important

being pelletierine (punicine) and isopelletierine, both of which are liquid at ordinary temperatures. The alkaloids, which may be present to the extent of about 1 per cent., occur in the bark as tannates and apart from this small proportion of combined tannic acid there is some 20 per cent. additionally present which confers upon the drug a powerful astringent action. The bark used to be administered in the form of a decoction, but this practice has been almost entirely superseded by the employment of the isolated mixed alkaloids as tannates.

PELLETIERINE TANNATE

A mixture of the tannates of the alkaloids obtained from pomegranate bark is officially known as pelletierine tannate. It may be prepared by mixing the ground bark with milk of lime, percolating with water, extracting the percolate with chloroform and shaking the chloroformic solution with dilute sulphuric acid. After separation, the acid liquor is neutralised and a solution of tannic acid added, when the sparingly soluble alkaloidal tannates are precipitated and, after being collected and washed, are dried at a gentle heat. Pelletierine tannate occurs as a light yellow, odourless, amorphous powder possessing an astringent taste. It is administered suspended in water in doses of from 5 to 8 grains. When given on an empty stomach and followed after a few hours by a brisk purge it serves as an excellent remedy for tape worm infection since pelletierine exerts a specific vermicidal action on this group of parasites, although it is of little service for removing other types of intestinal worms. Caution is necessary in the administration of pelletierine since large doses induce giddiness, weakness of the limbs and temporary disturbance of the vision.

ARECA NUTS (BETEL NUTS)

The seeds of *Areca Catechu*, a palm cultivated in tropical India and the Philippines, are about 2·5 cm. long and have the shape of a short rounded cone. The chief constituent, and the one upon which their action as a vermifuge depends, is the liquid alkaloid arecoline; besides small quantities of other inactive alkaloids the drug also contains a proportion of a red amorphous tannin together with fixed oil, resin and mucilage.

The drug is used almost exclusively in veterinary medicine as a vermifuge for tape worm. It is usually administered in the form of a confection consisting of the powdered seed mixed with honey, syrup or butter. The hydrobromide of the isolated alkaloid, arecoline, is sometimes employed instead of the whole drug. In addition to acting as an anthelmintic arecoline induces myosis, or contraction of the pupils, and in this respect resembles pilocarpine.

OTHER TÆNICIDAL DRUGS

Before leaving the subject of tænicides, or substances employed for the destruction of tape worms, three further vegetable drugs demand brief mention which, although not so widely employed as those discussed above, are still used extensively in certain localities.

KOUSSO, which was included in the 1914 issue of the British Pharmacopœia under the name Cusso, consists of the dried panicles of the pistillate flowers of *Brayera anthelmintica*, a tree indigenous to North-Eastern Africa and cultivated in Abyssinia. It occurs in commerce as cylindrical rolls or "hanks" about 60 cm. long, bound round with a flexible stem, and of a dull reddish colour. Occasionally, kousso, consisting of the loose, dried flowers stripped from the panicles, is offered for sale,

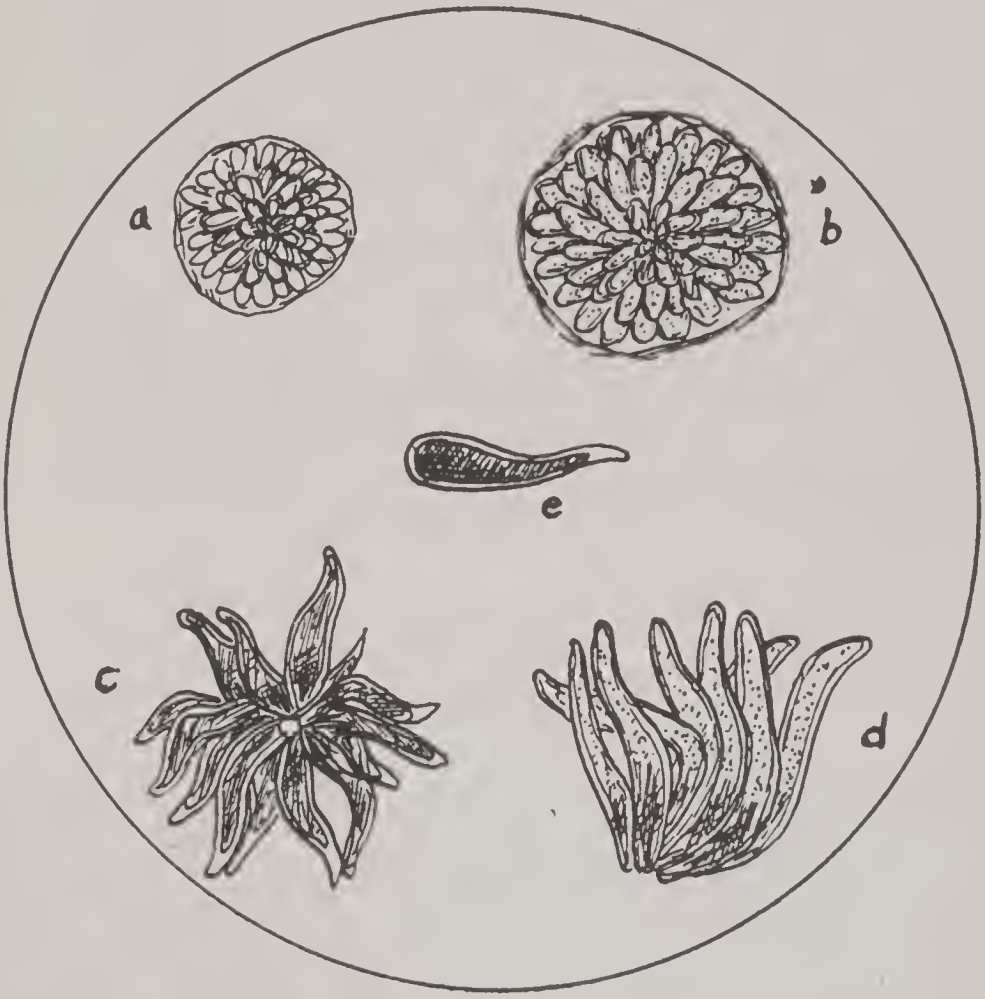


Fig. 4.—KAMALA AS SEEN UNDER THE MICROSCOPE AND MAGNIFIED APPROXIMATELY 200 DIAMETERS

a, gland viewed from below; *b*, gland viewed from above; *c* and *d*, clumps of hairs separated from glands; *e*, an individual hair.

but this variety is usually inferior, as it generally contains an admixture of the less active staminate flowers. The important constituent of this drug is a yellow amorphous substance termed kosotoxin, an extremely active vermifuge which is chemically similar to the filicic acid contained in male fern. The drug is administered in the form of an unstrained 1 in 16 infusion, the dose of 4 to 8 fluid ounces being given on an empty stomach and preceded by a purge. It is considered to be less certain in its action than extract of male fern, and on that account is now regarded as a drug of only secondary importance.

KAMALA consists of the glands and hairs covering the fruits of a small tree called *Mallotus philippinensis* which is widely distributed through India and the Malay Archipelago. The small capsular fruits are densely covered with a reddish-brown powder which, when detached by rubbing, and sifted to free it from mechanical impurities, constitutes the drug. It consists of minute red glands, from 0·04 to 0·1 mm. in diameter, with which are associated nearly colourless tufts of hairs as shown in Fig. 4. The physiologically active principle of kamala is called rottlerin, which is chemically allied to filicic acid and to kosotoxin. The drug is given in doses of about 100 grains mixed with honey or treacle or made into a draught with mucilage of gum acacia and water.

EMBELIA. In India and the Eastern Colonies the dried powdered fruit derived from either of two indigenous shrubs, *Embelia ribes* and *E. robusta*, is employed as a tænicide. The drug consists of spherical fruits about 4 mm. in diameter varying in colour from red to nearly black. The active principle, which is present to the extent of about 2·5 per cent., is termed embelic acid and can be isolated in the form of golden-yellow lamellar crystals.

SANTONICA

We now come to the most important remedy for the treatment of round worm and thread worm infection. Santonica, or wormseed, consists of the dried unexpanded flowerheads of *Artemisia cina* and other species of *Artemisia* (N.O. Compositæ), small perennial plants which are widely distributed throughout Europe and Asia. The important constituent of this drug is the crystalline bitter lactone, santonin, which is present to the extent of 0·5 to 3 per cent. Santonica itself is not employed in medicine, the herb being entirely utilised as a source of santonin, for which purpose it is collected in Turkestan, many parts of India and in Russia.

Determination of Santonin in Santonica

A number of procedures have been suggested for the determination of santonin present in santonica and the following technique is due to J. Coutts.

A weighed quantity (14 gm.) of the dried, coarsely powdered drug is treated with 140 ml. of pure benzene, the mixture being shaken at frequent intervals during 6 hours, and then 101 ml. of the solvent is filtered. The filtrate is transferred to a separator and shaken briskly with 35 ml. of an 8 per cent. aqueous solution of sodium carbonate. When the two immiscible liquids have separated 80·5 ml. of the benzene solution, corresponding to 8 gm. of the sample, is decanted into a flask and the solvent distilled off on a water-bath. The dry residue, which contains the santonin together with resinous extractive material, is treated with 60 ml. of a saturated solution of barium hydroxide at 95° C. and the mixture immediately filtered. The flask and filter paper are washed with two portions each of 10 ml. of saturated solution of barium hydroxide at 95° C., and the original filtrate and washings mixed in a suitable flask which is plugged with cotton-wool. When this solution is cool it is made slightly acid by the addition of 5 ml. of hydrochloric acid (25 per cent.) and then set aside for 24 hours in order to allow the santonin to crystallise, the mixture being occasionally gently agitated. The crystals are collected in a tared Gooch crucible (see page 130), any crystals remaining in the flask being washed into the crucible with small portions of the filtrate. Finally, the crucible and crystals of santonin are washed with 10 ml. of cold water and then dried to constant weight at 100° C.

SANTONIN

Santonin occurs in colourless, odourless, shining, flat, rhombic prisms which melt at 170° C. When exposed to daylight it assumes a yellow colour. It is sparingly soluble in cold water, but dissolves readily in organic solvents and in solutions of alkali hydroxides.

When taken internally, santonin is liable to induce a disturbance in the perception of colour, and illuminated objects appear to have a yellowish hue. In large doses santonin induces headache, nausea, vomiting, and sometimes convulsions. It may be administered in 1-grain doses suspended in a mixture with compound powder of tragacanth or as tablets containing 1 grain each of santonin and calomel. The 1914 issue of the British Pharmacopœia included a lozenge containing 1 grain of santonin in a simple basis consisting of sugar with gum acacia as binding agent. It is best to give the dose in the evening as the possible onset of yellow vision and vertigo is less likely to be troublesome: the administration should be followed in the morning with a castor oil or a saline purge.

Notes on Round Worms and Thread Worms

The round worm, *Ascaris lumbricoides*, is a commonly occurring human parasite somewhat resembling the ordinary earthworm in shape. The adult organisms live in the upper part of the intestine, the female worms measuring from 6 to 12 inches in length, while the males are smaller, rarely reaching 10 inches. The body is cylindrical in shape, tapering gradually towards each end, the tail of the male being curled while that of the female is straight. In colour they are yellowish or greyish-white, sometimes tinged with red, and when alive have a semi-translucent appearance. The mouth at the head end is surrounded by three small lips which are provided with rows of microscopic teeth by which the worm sometimes holds on to the lining of its host's intestine ; although it does not normally cause wounds, it may sometimes feed on the blood.

The female produces many millions of eggs each of which has a thick, clear inner shell covered over by a yellow, or brown, albuminous coat ; they usually measure about 0·06 mm. in length by about 0·04 mm. in breadth, and hence are easily seen when a portion of infected fæces is examined under the microscope. Under cool, moist conditions active embryos develop within the eggs in from 2 to 3 weeks and, if at this stage they are eaten by a suitable host, especially man or pig, the embryos hatch out in the small intestine, penetrate the mucous membranes and are carried by the blood stream to the liver, then the heart and then the lungs. Here they burrow out and make their way through the trachea, throat and œsophagus back to the intestine, meanwhile, in the 10 days occupied on this journey, having grown in length from about 0·2 mm. to 2 or 3 mm. The young worms then grow to maturity in 2 to 3 months.

In rare cases where the infection has been heavy, the migration of the larvæ through the lungs results in pneumonia ; again, cases have been known in which hundreds of worms have become entangled in masses which have resulted in intestinal obstruction. Usually, however, only a small number of worms, often two, establish themselves, and the host may not even be aware of their existence beyond experiencing a general feeling of debility which is usually attributed to some other cause. Occasionally the worms migrate to other parts of the body, setting up organic disorders, while sometimes they emerge from the nose or are vomited by the horrified patient.

Santonin generally proves to be an effective remedy for ascaris infection, and even when it does not actually kill the parasites it so lowers their vitality that they are unable to resist the movements of peristalsis and are consequently voided by the purge which is given after the anthelmintic.

The thread worm, or pin worm, is a very commonly occurring and widely distributed intestinal nematode worm belonging to the sub-order Oxyurata and known as *Enterobius* (*Oxyuris*) *vermicularis*. The adult

worm lives in the cæcum and the females, which are the only forms usually seen, are 8 to 13 mm. long and have white, cylindrical bodies tapering to a fine point at the tail-end. They can be observed actively wriggling in the freshly passed fæces of an infected person. The male worms are only 2 to 5 mm. long and have a curled tail and, being much less numerous than the females, are not so readily perceived. As eggs develop in the females the worms release their hold in the intestine and pass out of the body with the fæces or voluntarily migrate through the anal passage, causing intense itching in the process. Contact with the air stimulates the parasites to deposit eggs, and eventually the bodies of the worms dry and explode, liberating the remaining eggs in showers. The eggs are clear, unstained objects about 0·05 mm. long and if they find their way to the mouth of the infected person, or of another individual, they develop into adult worms and thus complete their life cycle. For this infection, which very commonly attacks children, santonin is the remedy of choice, and speedy destruction and expulsion of the worms generally follows on its administration.

SPIGELIA

The rhizome and rootlets of the Carolina pink, *Spigelia marilandica*, a native of the southern United States, is sometimes used as a remedy for ascaris infection. The plant is also known as the Indian pink and the drug is sometimes referred to as pink root. The chemical nature of the active constituent is not known, but it appears to be an acrid, bitter substance which is soluble in water and in alcohol, but insoluble in ether. The drug also contains a poisonous alkaloid, spigeline, while among other constituents are included a volatile oil, tannin, and resinous material. It is administered in powder or as an infusion mixed with purgatives and aromatics such as senna and fennel or, alternatively, a 1 in 1 liquid extract made with 49 per cent. alcohol may be used for compounding; the dose should be followed by a saline purgative. Spigelia is inclined to give rise to unpleasant toxic symptoms and it is now of minor importance.

Fig. 5.—Cowhage

Hairs from the fruit of *Mucuna pruriens*. A, entire elements magnified about 50 diameters; B, apex of a hair under a higher magnification Note the extreme sharpness of the point: a needle, viewed similarly, would appear to be quite blunt.

COWHAGE (MUCUNA)

Cowhage, or cowitch, is of interest in that it was at one time occasionally used as a vermifuge, its action in this respect being entirely mechanical. It consists of the hairs attached to the fruit of a leguminous climbing plant which grows in India and in the tropical parts of Africa and America. The drug occurs as a loose, yellowish-brown felted mass of hairs each of which consists of one thin-walled, sharply pointed cell about 3 mm. long (see Fig. 5). Cowhage is an unpleasant substance to handle owing to the persistent irritation that results from contact with the needle-shaped hairs. When given as an anthelmintic it is mixed with honey or treacle, its action depending upon the physical injury which the sharp hairs are able to inflict upon the worms. It is sometimes employed in this connection in veterinary practice, but in human medicine its use is confined to the occasional preparation of a rubefacient ointment to produce external counter-irritation.

CHENOPODIUM

In concluding this account of anthelmintics it may be observed that hook worm infection, which is an extremely troublesome parasite of man and widely distributed in tropical regions, was generally treated with chenopodium oil (or wormseed oil) obtained by distillation from the crushed fruits of *Chenopodium ambrosioides*. The fruit itself, often referred to as American wormseed, is rarely employed, although the powdered seeds used to be administered for the expulsion of round worms. The detailed discussion of volatile oils is beyond the scope of this book, but it may be of interest to observe that the oil from this drug has proved to be of great value in helminthological practice. However, in 1921 M. C. Hall observed that carbon tetrachloride was even more effective for the destruction of hook worms and the extensive adoption of this treatment has done much towards mitigating one of the major scourges of the tropics.

Chapter XX

DEMULCENTS, FLAVOURING AND COLOURING AGENTS

IT is convenient to consider drugs belonging to the above classes in one chapter, since the three effects may be said to have something in common. Thus the demarcation between a demulcent and a flavouring agent is not clearly marked, since liquorice may be considered as important under both headings while the water-soluble gums, which constitute the principal demulcents, contribute to the elegance and palatability of medicinal mixtures containing insoluble substances or emulsified oils. Even a pleasing colour may be said to augment the value of a medicine by inspiring the patient's confidence in the remedy.

DEMULCENTS

A number of colloid substances, such as gums, dextrins and starches, owe their medicinal value to the mechanical protection they afford to inflamed, or otherwise sensitive, surface tissues. Although a mucilage of a gum may have no taste or odour in itself it is, nevertheless, capable of influencing the taste of other substances mixed with it. Thus sugar dissolved in a mucilage tastes less sweet than an aqueous solution of equivalent strength. Again, the raspberry contains more acid and less sugar than the currant, but in the former the acid taste is concealed by the presence of a high proportion of colloids, whence the raspberry is regarded as a sweet fruit and the currant as an acid one. The same principle is illustrated in the case of ice cream which, owing to the colloidal substances which it contains, does not feel so cold on the tongue and throat as frozen water. Demulcents are employed to cover inflamed surfaces and as vehicles for other drugs. In acute irritant poisoning they are of value, since they protect the wall of the stomach from the effects of the poison.

LIQUORICE (GLYCYRRHIZA)

Liquorice consists of the peeled root and underground stem of various species of *Glycyrrhiza*, a leguminous plant widely distributed over Southern Europe and imported from Spain and Russia, as well as from Syria. The unpeeled drug is also recognised officially in the British Pharmacopœia. It occurs in long, yellow, cylindrical pieces from 1 to 2 cm. in thickness, having a nearly smooth but somewhat fibrous surface. The unpeeled root has a yellowish-brown, or dark brown, longitudinally wrinkled outer

layer. The chief constituent is from 2 to 7 per cent. of glycyrrhizin, an acidic glucoside with a sweet taste. In addition, the drug contains sugar, starch, proteins, fat and resinous substances.

Pharmacy of Liquorice

Extract of liquorice is made by percolating the powdered root with chloroform water, boiling the percolate for a few minutes, setting aside for some hours to allow the sediment to settle and evaporating the supernatant liquid to the consistency of a soft extract. Ordinary commercial liquorice extract is often moulded into flattened cylindrical rolls or into sticks. Extract of liquorice is used in pills as an excipient and, when excess of moisture is removed by evaporation, as "liquorice pellets," with or without menthol. Such pellets, as well as lozenges and pastilles, containing a basis of liquorice extract together with ammonium chloride and oil of anise, are all popular remedies for coughs.

The initial stages in the preparation of liquid extract of liquorice are the same as above but, instead of reducing the percolate to a soft extract, it is only evaporated until its specific gravity attains 1·2, and it is then allowed to cool and diluted with one-fourth of its volume of rectified spirit. This is a widely used preparation not only as a constituent of cough mixtures, where its demulcent action is so valuable, but also as a flavouring agent to disguise the taste of nauseous medicines such as the alkali iodides, ammonium chloride, quinine and liquid extract of cascara. It is incompatible with all acidic substances owing to the precipitation of the glycyrrhizin.

Compound liquorice powder has already been discussed in connection with the pharmacy of senna (page 116). Most of the remaining preparations of liquorice are of lesser importance, but the drug is widely employed in numerous proprietary medicines as well as in many elixirs, mixtures, pastilles and lozenges officially recognised by various foreign pharmacopœias.

Ammoniated Glycyrrhizin

This substance occurs in the form of dark brown, odourless scales having a very sweet taste. It is used as a substitute for extract of liquorice for flavouring, 1 grain being sufficient for 6 fluid ounces of a neutral mixture. It is prepared by macerating powdered liquorice root with very dilute ammonia, percolating with water, precipitating the percolate with dilute sulphuric acid, collecting and washing the precipitate, redissolving in very dilute ammonia, evaporating to a thin syrup, painting on to plates, drying and scaling. It is advisable to precipitate with acid a second time before proceeding with the final evaporation.

WATER-SOLUBLE GUMS

A number of natural plant products which form mucilaginous colloidal solutions in water serve as useful demulcents and are extensively employed in pharmaceutical practice. The names and principal characteristics of the more common products belonging to this group of substances are presented in Table XIV. Chemically, gums consist of mixtures of complex carbohydrates; on treatment with warm dilute mineral acids the mucilaginous property is destroyed and the gums are largely converted into sugars.

Of the gums mentioned in Table XIV acacia and tragacanth are the most important. The former is employed in the preparation of demulcent

TABLE XIV.—THE MORE COMMONLY OCCURRING WATER-SOLUBLE GUMS

Name	*Source*	*Mode of Occurrence*	*Remarks*
Acacia ..	Certain species of *Acacia*, small trees indigenous to East and West Africa	Rounded or ovoid pale yellowish tears or angular fragments	Acacia is a variety of gum arabic and is official in the British Pharmacopœia.
Agar-agar (Japanese Isinglass)	Seaweeds which flourish off the coasts of Japan	Transparent straw-shaped strips or in stouter quills. Sometimes as a powder	When taken, is not absorbed but swells in the intestine and is sometimes successfully employed in treating chronic constipation.
Ghatti Gum (Indian Gum)	Exudation from wood of *Anogeissus latifolia*, a large tree indigenous to India and Ceylon	Dull, rough surfaced translucent tears, or vermiform pieces	A useful substitute for acacia.
Karaya (Sterculia Gum)	Exudation from *Sterculia urens*, a tree growing in India	Irregular striated, often vermiform, white or pinkish-brown pieces with a distinctly acetous odour	Often used in place of tragacanth.
Tragacanth..	Exudation from stem of *Astragalus*, a shrub growing in Persia and Turkey	Thin, white or cream, horny, translucent flakes	Official in the British Pharmacopœia.

cough mixtures, as a suspending agent for the dispensing of heavy powders, as an excipient for pills and also as an ingredient of the official basis for lozenges. The official mucilage of acacia is made by dissolving the washed gum in chloroform water. Another important official preparation is the injection of sodium chloride and acacia, which consists essen-

tially of an isotonic salt solution (0·9 per cent. of salt in water) containing 6 per cent. of the gum. This preparation is administered by intravenous injection in order to prevent collapse due to loss of blood, the acacia serving to increase the viscosity of the preparation and to delay its elimination through the kidneys. Acacia is a valuable ingredient of cod-liver oil emulsion, in which it acts as a stabiliser, and it is largely employed for this purpose in the manufacture of many emulsified preparations.

Tragacanth is no less important than acacia and is extensively used in pharmacy as a suspending agent and as a stabiliser for emulsions. It is often employed in conjunction with acacia and the official compound powder of tragacanth consists of a mixture of these two gums in association with starch and sugar.

OTHER DEMULCENT DRUGS

It will be sufficient to give in tabular form a further selection of drugs belonging to this category since detailed descriptions in a work of this kind are unnecessary and would be tedious to follow. All the drugs in Table XV contain more or less mucilaginous material to which they owe their medicinal value.

TABLE XV.—DRUGS USED FOR THEIR DEMULCENT ACTION

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Application*	*Principal Preparation*	*Remarks*
Coltsfoot (Tussilago)	Flower or Leaf	Domestic remedy for coughs	Syrup (from flower), Decoction (from leaf)	Farfara is a Latin synonym.
Couch Grass (Agropyrum)	Rhizome ..	Demulcent diuretic for diseases of the genito-urinary tract	Decoction	Sometimes called Triticum.
Figs (Ficus) ..	Fruit ..	Administered with other laxatives. Used in the preparation of Confection of Senna, B.P.	Syrup ..	The Syrup is a constituent of many proprietary laxatives.
Iceland Moss (Cetraria)	Whole Plant (a lichen)	Demulcent nutrient ..	Decoction	Used as a food.
Irish Moss (Chondrus)	Thallus (a seaweed)	Remedy for coughs and invalid food	Decoction	Also used for clarifying beer.
Ispaghula (Ispaghula)	Seed	For diarrhœa and dysentery. Much used in the East	Decoction	Used as the equivalent of linseed in India.

TABLE XV.—DRUGS USED FOR THEIR DEMULCENT ACTION—*continued*

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Application*	*Principal Preparation*	*Remarks*
Linseed (Linum)	Seed	Treatment of coughs and bronchitis	Decoction and Poultice	Official in B.P. 1932.
Marshmallow (Althæa)	Peeled Root ..	For coughs ; also used externally as a fomentation and as an excipient for pills	Decoction	Guimauve is a synonym for this drug.
Prunes (Prunum)	Fruit	Used in the preparation of Confection of Senna, B.P.	—	—
Psyllium (Psyllium)	Seed	Treatment of chronic constipation	—	Seeds are taken dry or mixed with water.
Quince (Cydonia)	Seed	For dysentery and as a constituent of eye lotions	Decoction	The Mucilage is used as a suspending agent.
Sassafras Pith (Sassafras Medulla)	Pith of stems	To increase viscosity of eye lotions	Mucilage ..	—
Slippery Elm (Ulmus Fulva)	Bark	Demulcent for the intestines and poultice for ulcers and whitlows	Enema and Poultice	—
Sweet Almond (Amygdala Dulcis)	Seed	Ingredient of cough mixtures	Compound Powder	The compound powder contains acacia and sugar.

FLAVOURING AGENTS

Cassia, tamarinds and manna may conveniently be mentioned under this heading, although they owe their virtue only in part to flavour since, in addition, they are all mild laxatives. The first two are not usually prescribed alone, but find an important place in pharmacy as constituents of the official confection of senna. Figs and prunes, already mentioned in Table XV, may also be regarded as laxative flavouring agents, the latter being used in the preparation of confection of senna, while the former is widely used as a basis for the manufacture of laxative syrups.

CASSIA PODS

This is the fruit of *Cassia Fistula*, a leguminous tree indigenous to India. The ripe pods have the appearance of chocolate-brown, nearly straight, cylindrical rods varying from about 35 to 50 cm. in length and

from 18 to 25 mm. in diameter. The pods contain a nearly black viscid pulp which has a sickly odour and sweetish taste, and it is this substance which is included as an official drug in the British Pharmacopœia and which is employed in the preparation of confection of senna ; it contains oxymethyl-anthraquinones and more than half its weight consists of sugars. The pulp is removed by percolating the crushed pods with distilled water, straining the percolate and evaporating it on a water-bath to the consistency of a soft extract.

TAMARINDS

Tamarinds are the preserved fruit of the tamarind tree which is indigenous to Africa but is cultivated throughout India and the West Indies. The leguminous fruit varies from 5 to 20 cm. in length, and has a rough, brownish skin, the interior containing large seeds together with pulpy material which is traversed by branching fibres. After removal of the skin, the fruits are preserved by treatment with hot syrup and the candied product constitutes the official drug. It occurs as a reddish-brown, moist, sugary mass, in which the fibres and seeds are conspicuous. The original pulp contains a considerable proportion of tartaric acid and invert sugar, while, of course, the preserved material also contains the added cane sugar. When infused with water tamarinds form an agreeable drink which is sometimes administered in feverish conditions, but the drug is principally employed in the preparation of confection of senna.

MANNA

According to the dictionaries the name of this substance is supposed to be a corruption of the Hebrew *man hu* or What is this ? The question being asked by the Israelites when they first saw it as " a small round thing, as small as the hoar frost on the ground." The term is applied to the saccharine exudation derived from a number of different plants, but the material of commerce is derived from small trees belonging to the genus *Fraxinus* which are cultivated for the purpose in Sicily. The best variety is known as flake manna and occurs in yellowish-white, brittle, stalactitic masses from 10 to 15 cm. long and about 2 cm. wide, and having a triangular section, the side by which they adhered to the stems of the trees being smoother than the others and slightly concave. It has a faint, agreeable odour and a sweet taste. In wet seasons the exudation drops from the trees and is caught upon tiles or cactus leaves yielding agglutinated fragments darker in colour and of inferior quality to flake manna. The chief constituent is the hexahydric sugar alcohol, mannitol (mannite), of which it contains 40 to 60 per cent., the remainder comprising various sugars, mucilage and water. Manna is used as a gentle laxative for children, and it is sometimes administered as a compound syrup containing senna and fennel or is used to sweeten dill water.

LEMON PEEL AND BITTER-ORANGE PEEL

Fresh lemon peel and both fresh and dried bitter-orange peel are official in the British Pharmacopœia 1932, and they are employed as flavouring agents although they may equally well be classed as bitters. Two galenical preparations of lemon peel are officially recognised, the syrup and the tincture, both of which are used to flavour mixtures, the former being particularly suitable for medicines containing acids. The official tincture of orange and syrup of orange are made from fresh bitter-orange peel (Aurantii Cortex Recens) while the concentrated infusion and the fresh infusion are prepared from dried bitter-orange peel (Aurantii Cortex Siccatus). . The infusions are useful as ingredients of bismuth indigestion mixtures. An orange wine, made by the fermentation of a saccharine solution to which fresh bitter-orange peel has been added, was official in the B.P. 1914. The quinine wine of the same authority was directed to be made by dissolving 0·23 per cent. of quinine hydrochloride in the orange wine, while a wine of iron citrate contained 1·8 per cent. of iron and ammonium citrate in the same vehicle. These preparations are still quite widely employed. The British Pharmaceutical Codex includes a detannated preparation made by macerating orange wine with 0·15 per cent. of powdered gelatin for 24 hours with frequent agitation followed by decantation ; it is useful for making mixtures containing ingredients that are incompatible with tannin. Lemon peel and dried bitter-orange peel are included in the formulæ for the fresh and concentrated compound infusion of gentian of the B.P. 1932.

COLOURING AGENTS

The principal colouring agents of vegetable origin are listed in Table XVI. Annatto is rarely employed for pharmaceutical purposes, being mainly used for colouring butter and various fats and oils. Cudbear is prepared by digesting the lichens with dilute solution of ammonia for several days, then drying the mixture and grinding the product. It is a purplish-red powder and is used for imparting a bright red colour to acid mixtures, for which purpose a solution of cudbear (Liquor Persionis) is prepared by extracting with boiling water or, alternatively, a tincture is employed. In alkaline solution cudbear assumes a purplish-red tint.

The use of saffron, which imparts a fine yellow colour to solutions, is limited by its high cost. Red sanders wood was official in the B.P. 1914 and was used for colouring the compound tincture of lavender of the same authority and this in its turn was an ingredient of arsenical solution, B.P. 1914. The arsenical solution of the present Pharmacopœia (B.P. 1932) is not coloured, while compound tincture of lavender has been omitted and red sanders wood is no longer an official drug.

Of the natural colouring substances, solution of cochineal (Liquor Cocci) is much more generally employed than any of the above vegetable

products. The cochineal insect is the source of carmine which is used to colour ointments, tooth powders, dusting powders and numerous cosmetic preparations. Owing to the tendency for cochineal to form unsightly precipitates in mixtures, synthetic dyes are now usually employed for colouring, Bordeaux B (Azorubrum) being used for red preparations and a mixture of tartrazine and orange G in glycerin and chloroform water (Liquor Flavum) for providing a yellow tint. Burnt sugar, or caramel (Saccharum Ustum), is widely used as a brown colouring, while chlorophyll is sometimes employed for imparting a green colour to soap, ointments and other fatty products.

TABLE XVI.—COLOURING AGENTS OF VEGETABLE ORIGIN

Name (Latin Name in Brackets)	*Plant Producing the Colour*	*Chief Geographical Source*	*Part of Plant Used*	*Remarks*
Alkanna, or Alkanet, Root (Anchusæ Radix)	*Alkanna tinctoria*	Hungary, Greece and Asiatic Turkey	Root ..	Contains about 5 per cent. of alkannin. Used for colouring oily toilet preparations.
Annatto (Annatta)	*Bixa Orellana*	East and West Indies and S. America	Seed ..	Consists of the dried pulp made from the seeds.
Cudbear (Persio)..	*Roccella tinctoria* and *R. Montagnei*	Canary Islands and Madagascar	Whole Plant (a lichen)	—
Dragon's Blood (Sanguinis Draconis)	*Dæmonorops propinquus* and *D. ruber*	Sumatra; also from *Dracæna Cinnabari*, Somaliland	Fruit ..	The red resin is shaken off the fruits. Mainly used for lacquers and varnishes but occasionally for plasters.
Red-Poppy Petals (Rhœados Petala)	*Papaver Rhœas*	Britain and Europe generally	Petals ..	Syrup of Red-Poppy is sometimes used to colour gargles, etc.
Red-Rose Petals (Rosæ Gallicæ Petala)	*Rosa gallica*	Europe ..	Petals ..	Acid Infusion of Roses is a red basis for alum or tannin gargles. Incompatible with alkalis.
Red Sanders Wood or Red Sandalwood (Pterocarpi Lignum)	*Pterocarpus santalinus*	India	Wood ..	Usually obtained as a coarse powder or in raspings.
Saffron (Crocus) ..	*Crocus sativus*	Spain, Austria, Italy; also Kashmir	Stigmas and tops of styles	—
Turmeric (Curcuma)	*Curcuma longa*	India, China, and Java	Rhizome	Mainly used in curry powders.

Chapter XXI

MISCELLANEOUS DRUGS AND VEGETABLE PRODUCTS USED IN PHARMACEUTICAL PRACTICE

THERE remains to be mentioned nearly two dozen vegetable drugs still occasionally employed but mostly of minor importance which, as it has not hitherto been convenient to discuss them, are now mentioned in tabular form.

TABLE XVII.—A MISCELLANEOUS SELECTION OF DRUGS OF MINOR IMPORTANCE

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Therapeutic Use and Remarks*
Absinthium or Wormwood (Absinthium)	Leaf and Flowering Tops	Tincture ..	Cerebral stimulant in neurasthenia; rarely employed.
Arnica (Arnica) ..	Flowers or Rhizome	Tincture of Arnica Flowers: Liniment(from rhizome): Tincture (from rhizome)	Externally for sprains and bruises.
Curare (Curara) ..	Extract from Bark	Injection ..	Occurs as a brittle black mass and contains intensely active alkaloids. Used by S. American natives as an arrow-poison for hunting. Has been employed for tetanus and hydrophobia.
Dulcamara or Bittersweet (Dulcamara)	Stems and Branches	Infusion ..	Domestic remedy for rheumatism but of doubtful value. Contains two saponins and an alkaloid.
Elaterium (Elaterium)	Dried Sediment from Juice of Fruit	Pill	Active principle is a crystalline body called Elaterin (about 30 per cent.) which is more generally used. Very powerful cathartic for treatment of cardiac and renal dropsy.

TABLE XVII.—A MISCELLANEOUS SELECTION OF DRUGS OF MINOR IMPORTANCE—*continued*

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Therapeutic Use and Remarks*
Euonymus Bark (Euonymi Cortex)	Root Bark ..	Extract incorporated into Pills	Mild cathartic. Euonymin is a powdered extract of the drug. Active principle is the crystalline alcohol, euonymol.
Eupatorium (Eupatorium)	Leaf and Flowering Tops	Infusion ..	Diaphoretic (causes the patient to perspire freely). Used at onset of influenza and muscular rheumatism.
Fœnugreek Seeds (Fœnum-Græci Semina)	Seed ..	—	Mainly used in veterinary practice. Used in Egypt as a febrifuge and digestive aid.
Gamboge (Cambogia)	Gum-resin ..	Compound Pill (with aloes, cinnamon, cardamom, ginger, etc.)	Powerful cathartic; occasionally used in dropsical conditions.
Green Hellebore Rhizome (Veratri Viridis Rhizoma)	Rhizome ..	Tincture ..	Powerful sedative; rarely prescribed. Is the rhizome of *Veratrum viride* and contains the same alkaloids as white hellebore (see page 183).
Iris or Blue Flag (Iris)	Rhizome and Root	Dry extract called Iridin.	Purgative; compounded in pills also containing euonymin.
Lactucarium or Lettuce Opium (Lactucarium)	Dried Latex	Tincture (1 in 2) and Syrup (1 in 10 of the tincture)	Cough sedative and mild hypnotic. Contains about 40 per cent. of lactucerin, a tasteless crystalline substance. There is no appreciable amount of alkaloidal material present. The whole fresh herb, *Lactuca virosa*, is also sometimes used in the form of an extract of its juice.
Leptandra or Culver's Root (Leptandra)	Rhizome and Root	Liquid extract. Leptandrin is a resinoid prepared by pouring tincture of leptandra into water then soparating and drying the precipitato	Cholagogue. Leptandrin is more generally used, compounded into pills with euonymin, podophyllin and extract of belladonna.

TABLE XVII.—A MISCELLANEOUS SELECTION OF DRUGS OF MINOR IMPORTANCE—*continued*

Name (Latin Name in Brackets)	*Part of Plant Used*	*Principal Preparations*	*Therapeutic Use and Remarks*
Pilewort or Lesser Celandine (Ficaria)	Whole fresh Herb	Ointment ..	An old remedy for hæmorrhoids.
Pyrethrum Root or Pellitory Root (Pyrethri Radix)	Root ..	Tincture and Lozenge	Tincture is applied locally for toothache and Lozenge is used as a sialagogue in dryness of mouth and throat. Is the root of *Anacyclus Pyrethrum* and should not be confused with pyrethrum flowers.
Stillingia (Stillingia)	Root ..	Liquid extract	Sialagogue and expectorant.
Sumbul (Sumbul) ..	Root ..	Tincture ..	Antispasmodic in hysterical conditions. Usually given with preparations of valerian.
Wood Charcoal (Carbo Ligni)	Wood charred without access to air. Willow charcoal generally used in Britain	—	Taken with treacle and water it is an excellent remedy for chronic biliousness as well as for some other forms of dyspepsia.
Zanthoxylum or Prickly Ash (Zanthoxylum)	Bark ..	Liquid extract	Diaphoretic; its action resembles that of guaiacum resin and it is used for similar purposes.

VEGETABLE PRODUCTS USED IN PHARMACEUTICAL PRACTICE

It is appropriate to conclude the foregoing account with a brief mention of a few products which, while not medicines in themselves, serve particular purposes in pharmacy.

GUTTA PERCHA is prepared by drying and purifying the latex of various species of *Palaquium* and *Payena. Leerii*, large trees indigenous to the Malay Archipelago and belonging to the Natural Order Sapotaceæ. The latex, obtained from the trunks of the trees, is allowed to coagulate, then purified by treatment with boiling water, the softened mass being formed into large flattened cakes. It is used in pharmacy for the preparation of traumaticin, which is a 10 per cent. chloroformic solution employed for the close application of medicaments, such as chrysarobin, to the skin (see page 180).

CHICLE GUM is the thickened latex from *Achras Sapota* (N.O. Sapotaceæ), indigenous to Mexico, Central America and the northern part of South America. It is somewhat similar to gutta percha, and is sometimes used for making thin dressing tissues but finds more extended use for the preparation of chewing-gum.

OLIBANUM, also known as **FRANKINCENSE**, is a gum-resin obtained from various species of *Boswellia*, small trees indigenous to Somaliland and Southern Arabia. It contains from 60 to 70 per cent. of resin, 25 to 35 per cent. of water-soluble gum (chiefly arabin) and 3 to 8 per cent. of volatile oil. Olibanum is occasionally used in the preparation of plasters and is nearly always included as an ingredient of incense.

SANDARAC, OR GUM JUNIPER, is a resin obtained from a small coniferous tree (*Callitris quadrivalvis*) growing in the mountainous regions of North-Western Africa. It occurs in pale yellow, brittle tears 5 to 15 mm. long, usually cylindrical in form. When chewed the resin breaks into a sandy powder which does not agglomerate into a plastic mass. Sandarac is largely employed in pharmacy for coating pills, a suitable solution being made by dissolving 1 part of resin in a mixture of 2 fluid parts of dehydrated alcohol and 1 fluid part of ether. In Australia another variety of sandarac is often used ; it closely resembles the ordinary resin but is derived from *Callitris verrucosa*.

Fig. 1.—GAMBOGE

The gum-resin is obtained from a tree growing in Siam, Cambodia and Cochin China. As it exudes it is received into large hollow bamboos, thence transferred to smaller ones in which it is allowed to harden. It occurs in solid rolls or hollow cylinders, the drug in the latter form being known as pipe gamboge.

MASTIC is collected on the island of Chios in the Grecian Archipelago by puncturing the bark of a small tree, *Pistacia Lentiscus*, and allowing the oleo-resin to exude and harden. It occurs in small, hard, pyriform or nearly globular tears about 5 mm. long which are pale yellow in colour, clear and glassy when fresh but becoming dull and dusty on the surface during storage. It has an aromatic odour and agreeable taste, and, when chewed, breaks into sandy fragments which agglomerate into a plastic mass (*cf.* sandarac). Solutions of mastic in alcohol, ether or chloroform are used, applied on cotton-wool, as temporary stoppings for carious teeth and it is also employed as an ingredient of surgical varnishes.

DAMMAR is a resin derived from the Amboyna pine which is cultivated

in the East Indies and it is sometimes termed Manila copal or mastic. It occurs in pale amber-coloured nodules usually 3 to 6 mm. in diameter, the exterior being coated with white powder. It is readily friable and adheres only feebly when warmed in the hand. Dammar is but little used in pharmacy but occasionally finds a place as a constituent of plaster masses.

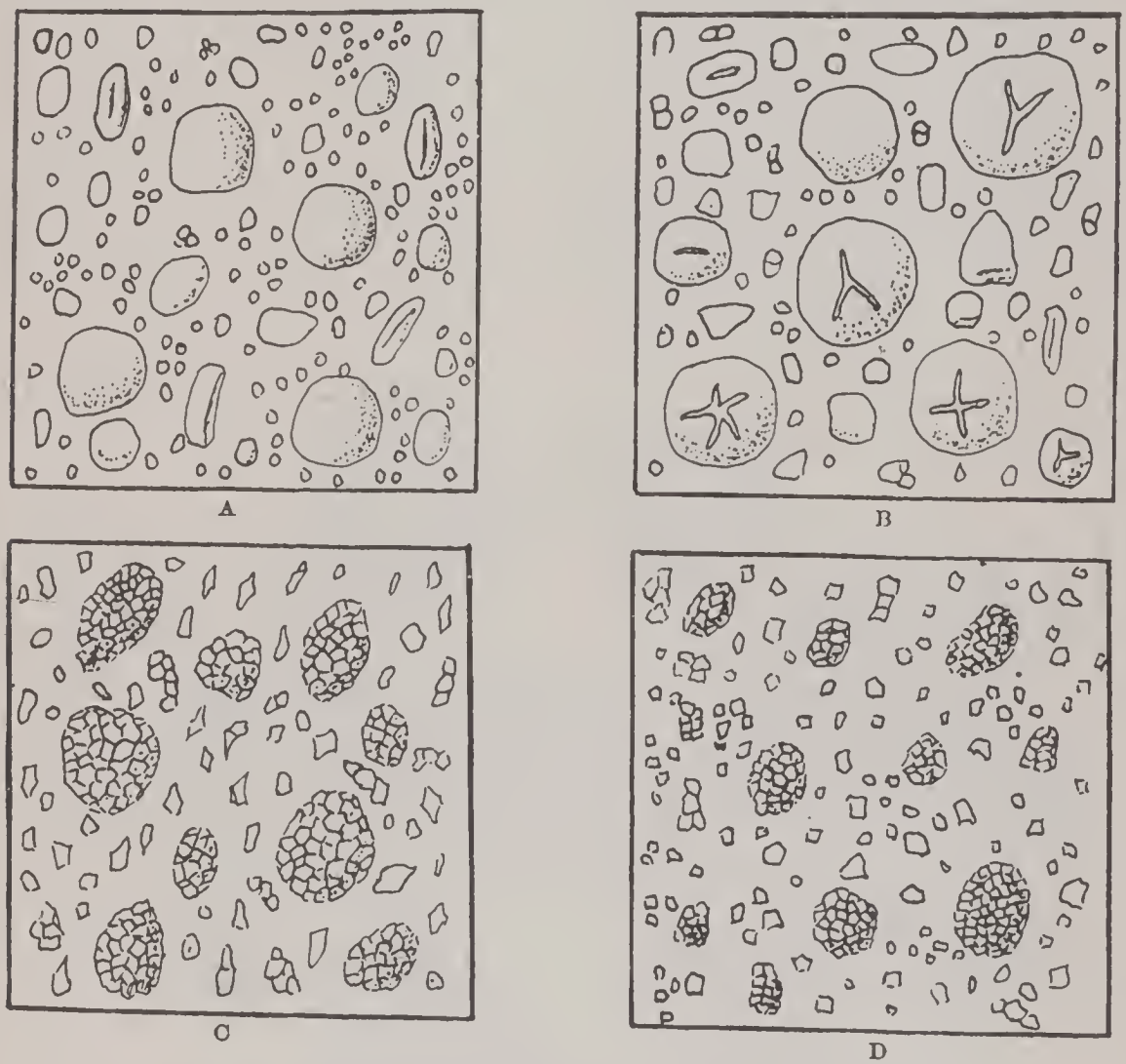


Fig. 2.—STARCHES AS SEEN UNDER THE MICROSCOPE

A shows wheat starch, and it will be noted that the grains vary considerably in size. Measurements of microscopical objects are expressed in micra, a micron, μ, being one-thousandth of a millimetre (0·001 mm.). The small grains of wheat starch vary from 2 to 8 μ in diameter and the large grains from 25 to 40 μ. Rye starch, B, is characterised by a fissured stellate hilum having three to five rays : size of small grains, 3 to 10 μ ; large grains, 40 to 50 μ. Oat starch, C, forms many compound grains from 35 to 50 μ in length : some of the simple grains are characteristically spindle-shaped and all average about 10 μ in diameter. The simple grains of rice starch, D, are fairly uniform in size (4 to 6 μ), but are never spindle or lemon shaped : the compound grains readily disintegrate and may not be seen in all specimens.

COPAL OR GUM ANIMI is a fossil resin found on the east coast of Africa and shipped from Zanzibar. It occurs in pale yellow, reddish-brown or greenish-red pieces of varying size, having a warty surface. It is occasionally employed as an ingredient of plasters but is mostly used

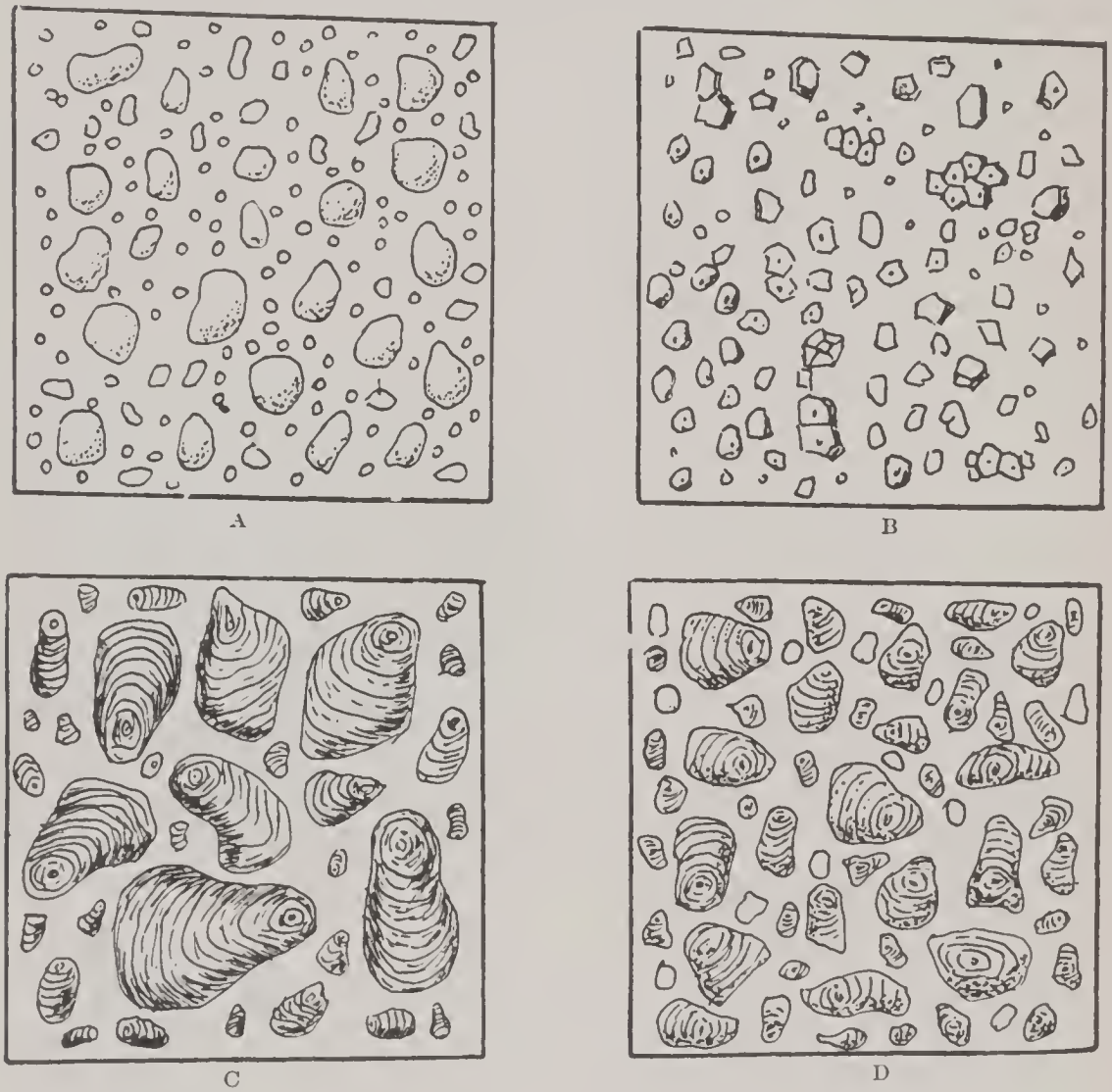


Fig. 3.—STARCHES AS SEEN UNDER THE MICROSCOPE

The grains of barley starch, A, are distinguished from those of wheat by their outline, which is less regular and often bears protuberances. The small grains vary from 2 to 8 μ in diameter and the large from 20 to 35 μ. They have no apparent hilum, but sometimes faint concentric striations can be seen. Maize starch, B, is readily recognised by the angular shape of the grains and the conspicuous hilum: they vary from 10 to 25 μ in diameter. Potato starch, C, forms grains, the large ones varying from 75 to 110 μ and the small from 15 to 25 μ in length, which are characterised by the presence of concentric striations. Maranta starch grains, D, bear numerous fine concentric striations and a rounded, linear or stellate, eccentric hilum; the smaller grains vary from 7 to 15 μ and the larger from 30 to 60 μ in length.

for making varnish. The latter may be prepared by heating the copal until frothing ceases, adding linseed oil, again heating and finally adding oil of turpentine to the cooled mixture.

KAURI GUM OR AUSTRALIAN COPAL is a resin obtained from *Agathis Australis*, a tree growing in the north of New Zealand, and it occurs in large pieces of a pale yellow or greenish-yellow colour possessing a balsamic odour. It is a useful constituent of dental waxes intended for taking impressions of the mouth.

CANADA BALSAM (TEREBINTHINA CANADENSIS) was formerly an ingredient of flexible collodion, but for this purpose it has been displaced by colophony. Its solution in benzene or xylene is used as a permanent mounting medium in microscopy. Canada balsam is an oleo-resin obtained from the balsam fir, *Abies balsamea*, a tree indigenous to the United States and Canada, and it occurs as a pale yellow, viscid liquid with an agreeable

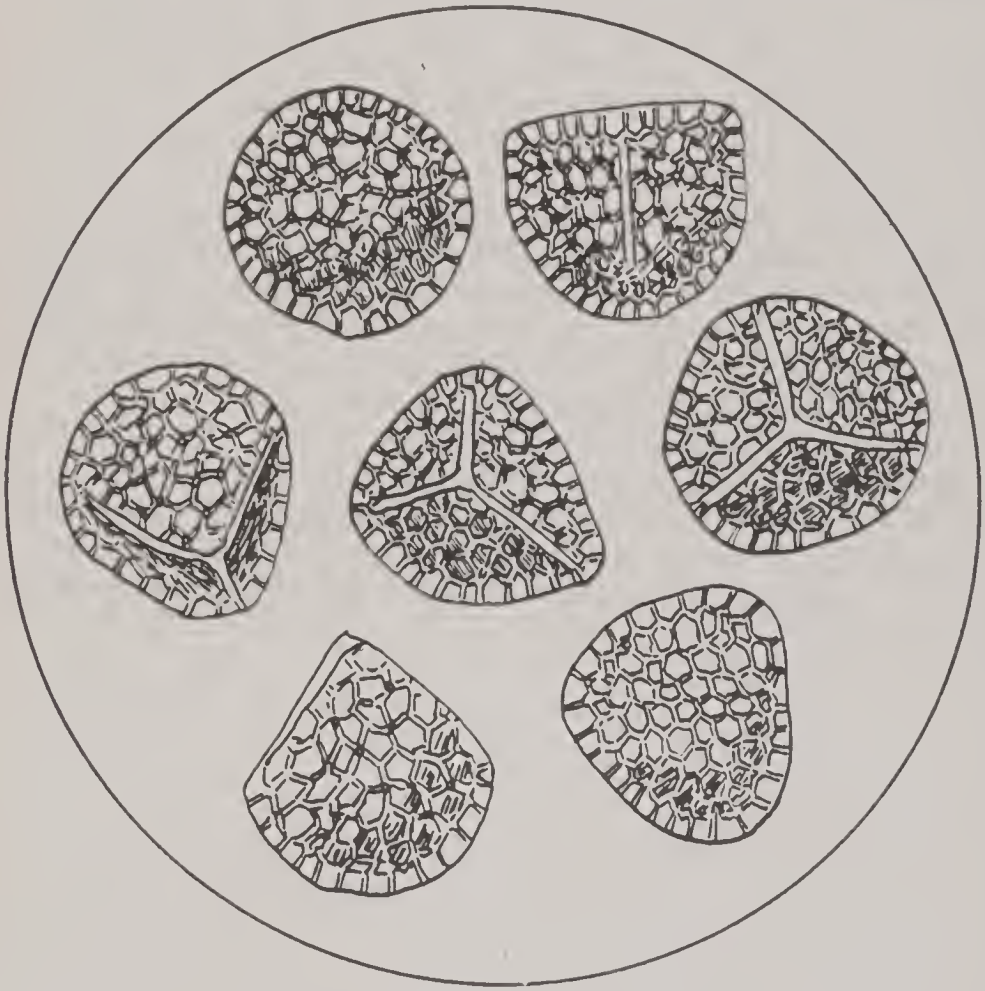


Fig. 4.—LYCOPODIUM AS SEEN UNDER THE MICROSCOPE

The spores have the shape of low, broad triangular pyramids resting upon a convex base and are covered by a delicate network of raised transparent ridges. Each spore is about 25 μ in diameter.

terebinthinate odour and bitter, acrid taste. On storage its viscosity increases and it dries to a hard, transparent varnish that shows no disposition to crystallise. Essentially, it consists of resin with from 16 to 24 per cent. of a volatile oil which is mainly lævo-pinene.

STARCH (AMYLUM), apart from its use as a demulcent and as an ingredient of mucilaginous preparations and dusting powders, is largely employed as an excipient for tablets. Starches from many sources are available in commerce and when examined microscopically it is seen that each plant produces grains of characteristic appearance; in this way it is generally possible to identify the origin of any given sample, although in some instances considerable experience is needed to do this with certainty. Maranta, or arrowroot, which is the starch from *Maranta arundinacea*, is especially favoured for making mucilaginous preparations.

ORRIS ROOT (IRIDIS RHIZOMA) is the rhizome obtained from various species of iris cultivated in Italy. Dried and powdered material of good quality possesses a pleasant and characteristic aroma and is largely used as an ingredient of dentifrices and toilet powders while, as already indicated on page 175, it is also employed in the preparation of rubber adhesive plaster.

LYCOPODIUM consists of the spores of the common club moss, a creeping plant indigenous to Europe, Asia and North America. It occurs as a pale yellow, mobile, odourless, tasteless powder which, by reason of its containing about 50 per cent. of fixed oils, floats on the surface of water without being wetted. It consists entirely of minute spores having the shape of a triangular pyramid with a convex base (see Fig. 4). Lycopodium is employed in pharmacy as a diluent for insufflations, as a basis for medicinal snuffs, and as a covering for pills. The particles of lycopodium are remarkably uniform in size and weight and T. E. Wallis has taken advantage of this to evolve an ingenious system of quantitative microscopy based on the fact that 1 mg. of the powder contains 94,000 spores.

Chapter XXII

GENERAL CONSIDERATIONS

BEFORE bringing to a close this brief survey of "the blest infusions that dwell in vegetives," it will perhaps be appropriate to offer a few observations of a general character. In these days, students of pharmacy, medicine and chemistry may well be inclined to regard the vegetable drugs as being old-fashioned medicaments which will soon be superseded by hormones, vitamins and synthetic chemicals. Actually, notwithstanding the great discoveries which have lately been made in the realm of hormone therapy coupled with the achievements of modern chemical and biochemical research, the principal vegetable drugs are not likely to be readily displaced. In assessing their true position in therapeutic practice it is important to realise that by reason of their accessibility their value to medicine was discovered long ago. Thus, knowledge of the value of cinchona for the treatment of fevers was first acquired by Europeans during the first half of the seventeenth century; the virtue of digitalis as a remedy for cardiac disease was originally investigated by William Withering, who published an account of his researches in 1785; and the use of opium dates back to classical times. The introduction into medical practice of these drugs, and of many others besides, was the subject of much debate and discourse such as to-day centres around the discovery of a new hormone or vitamin. When to these considerations is coupled the reminder that no complete substitutes have been found for the important vegetable drugs their true significance will be appreciated.

Again, even when treatment by the administration of the active principles in lieu of the galenical preparations is preferable, it is rarely economical and, at the present time, often impossible to produce them by chemical synthesis. Thus, quinine, digitalin, morphine, strychnine, cocaine, emetine, hyoscyamine, physostigmine, pilocarpine, ergometrine and many other highly important drugs are all extracted from their respective vegetable sources. It may be observed, however, that in some instances the value of these active principles for particular purposes can be enhanced by artificial modification: thus, emetine can be converted into insoluble emetine bismuth iodide which will pass through the stomach unchanged and decompose in the intestine where its action on the amœba of dysentery is required; morphine is transformed by acetylation into the less depressing but still powerfully sedative drug diamorphine; and hyoscyamine can be racemised to produce the less toxic and more generally useful alkaloid atropine.

The chemical structure of many complex plant principles is known with a fair degree of certainty and, although there are few instances in which their synthesis even on a laboratory scale is practicable, the knowledge of their constitution has been utilised by chemists who have been enabled to produce additional drugs of great value. Thus, the recognition of the fact that the quinoline ring forms an essential part of the quinine molecule led to attempts to prepare febrifuges from quinoline and from the allied bases isoquinoline and pyridine which resulted, in the earlier stages, in the production of 8-hydroxy-N-methyl—1 : 2 : 3 : 4—tetrahydroquinoline hydrochloride which possessed a marked antipyretic action and was placed on the market under the name kairine. However, it was found to induce unpleasant and dangerous secondary effects, and, following a series of investigations, L. Knorr in 1887 introduced another drug, antipyrine, which is still widely used under the name phenazone. At first Knorr regarded his new product as the derivative of a hypothetical base, quinizine, and as such it bore sufficient analogy to the physiologically active quinoline compounds to suggest the study of its therapeutic action. Subsequent investigation led its discoverer to assign to it a different structural formula and, in fact, it proved to be a substituted pyrazolone, but it was its supposed relation to kairine that suggested its clinical examination. Neither kairine nor phenazone is endowed with any specific action against the malarial parasite, but the practical value of the latter drug is too well known to require comment. Its therapeutic action is nearly free from injurious secondary effects and its success has given valuable clues in the development of other useful synthetic medicines, whence it is seen that attempts to imitate the physiologically active principle of cinchona bark has led to unexpected but highly fruitful results while, at the same time, quinine still remains the remedy of choice for the treatment of malaria.

Somewhat similar investigations were conducted with the object of producing synthetic local anæsthetics of low toxicity. Here again the known chemical structure of cocaine, the active principle of the coca leaf, served as the starting-point and, although many departures had to be made from the original suppositions, some highly successful new drugs have been evolved and to-day the regional anæsthetic amylocaine and the local anæsthetic procaine, both synthetic products, are much more generally employed than cocaine. In this case the use of the vegetable drug is being largely superseded but it has undoubtedly been of great value in supplying a ground plan upon which the organic chemist could commence to build.

It should not be assumed that the vegetable kingdom has been completely explored and that no further products of medicinal value can be discovered. On the contrary, much fruitful research is in progress. Thus, recent pharmacological and clinical work conducted by J. D. P. Graham has confirmed earlier observations as to the value of galenical

preparations made from the fruits of hawthorn (*Crataegus oxyacantha*) for the treatment of patients with cardiac lesions or chronic high blood-pressure. Other investigations have been directed to alkaloids derived from plants belonging to the genus *Erythrina*. The active principles of these plants induce curare-like effects and one of them, β-erythroidine, has proved to be of benefit in controlling the severity of the convulsions produced by the administration of leptazol (pentamethylene-tetrazole) in the shock treatment of schizophrenia and other mental diseases. The remarkable bacteriostatic substance penicillin, which is formed in cultures of the mould *Penicillium notatum*, is another example of a newly discovered substance of therapeutic value derived from the vegetable kingdom. It has been shown that purified penicillin when present in extreme dilution inhibits the growth of *Staphylococcus aureus* and *Streptococcus pyogenes*, and it is expected that the clinical investigation of this remarkable substance will lead to important issues. The foregoing are but three examples of contemporary studies on vegetable materials and it will not be inappropriate to remind the reader that pharmacologists and clinicians throughout the world are continually studying by scientific methods new plant products for their possible medicinal value, often selecting species peculiar to their own localities.

In one important respect the investigation of hormones appears to be a much more fruitful field of research than the corresponding study of vegetable drugs. The former is less empirical. Based on knowledge already supplied by the study of endocrinology, the modern investigator has some guide as to the probable effects of administering a newly discovered hormone or, alternatively, there is a clue as to where he may expect to find one secreted. On the other hand, although modern pharmacology has done much to systematise our knowledge of therapeutics the fact remains that so far as vegetable drugs are concerned it is still largely empirical. No one really knows why digitalis strengthens the contractions of the heart, why quinine is lethal to the parasite of malaria, why opium is a powerful sedative, why ergot possesses oxytocic activity. Eventually these questions will doubtless be answered, but a medicine is none the less valuable because the reason for its action is not understood and so, after considering all the advances which are taking place in materia medica, there would seem to be no valid grounds for supposing that the use of vegetable drugs will ever be superseded.

INDEX

(Figures in heavy type indicate main references)

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